

Combination Therapy Devices in Diabetes Management

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ABSTRACT

Diabetes management has evolved from isolated insulin injections and intermittent glucose checks to integrated systems combining continuous glucose monitoring, automated insulin delivery, and digital therapeutic support within unified platforms. Combination therapy devices -- hybrid closed-loop insulin pumps, dual-hormone artificial pancreas systems, sensor-augmented pen injectors, and AI-driven multi-therapy optimisers -- represent a paradigm shift toward holistic glycaemic management that coordinates monitoring, drug delivery, and behavioural intervention. This study presents the Combination Therapy Device Assessment Framework for Diabetes (CTDAF), evaluating five device integration levels -- standalone CGM with manual insulin adjustment, sensor-augmented pump therapy with low-glucose suspend, hybrid closed-loop single-hormone systems, dual-hormone closed-loop systems (insulin + glucagon), and AI-integrated multi-therapy platforms combining insulin delivery with GLP-1 dosing guidance and behavioural coaching -- across four glycaemic management tasks: time-in-range optimisation, hypoglycaemia prevention, glycaemic variability reduction, and patient burden minimisation. Our Diabetes Device Integration Score (DDIS) integrates time-in-range achievement, hypoglycaemia avoidance, variability control, device burden, and treatment satisfaction. AI-integrated multi-therapy platforms achieved the highest DDIS (0.928) through reinforcement learning algorithms that simultaneously optimised basal insulin, bolus recommendations, and GLP-1 timing to achieve 82% time-in-range with 1.2% time-below-range, while dual-hormone systems achieved the highest hypoglycaemia prevention (0.960) through automated mini-dose glucagon delivery that reduced time below 54 mg/dL by 78%.

Keywords: diabetes management; closed-loop; artificial pancreas; insulin pump; continuous glucose monitoring; dual-hormone; GLP-1; time-in-range; automated insulin delivery; reinforcement learning

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1. Introduction

1.1 The Evolution Toward Integrated Diabetes Technology

Type 1 and insulin-requiring Type 2 diabetes demand continuous therapeutic decision-making -- estimating carbohydrate intake, calculating insulin doses, anticipating exercise effects, and responding to glycaemic excursions -- that imposes a cognitive burden estimated at 180 additional health-related decisions per day (Polonsky, 1999). This burden, combined with the ever-present risk of hypoglycaemia from insulin overdosing, drives the persistent gap between recommended glycaemic targets (HbA1c < 7%, time-in-range > 70%) and achieved outcomes (mean HbA1c 8.4% in Type 1 diabetes, TIR 55-60% in real-world CGM data). The technological response has been progressive integration: from separate insulin syringes and fingerstick glucometers in the 1980s, through insulin pumps and CGMs as independent devices in the 2000s, to today's closed-loop systems where CGM data algorithmically drives insulin pump delivery with minimal patient intervention. The landmark NEJM trial of the Medtronic 780G demonstrated that hybrid closed-loop therapy achieved 75% TIR versus 60% for sensor-augmented pump therapy in Type 1 diabetes (Brown et al., 2019). The emerging frontier extends integration beyond insulin to incorporate GLP-1 receptor agonist dosing, behavioural interventions, and multi-hormone delivery within AI-coordinated platforms that manage the complete therapeutic regimen rather than individual drug delivery (Boughton and Hovorka, 2021).

1.2 Five Integration Levels

Five integration levels represent the current technology spectrum. Standalone CGM with manual adjustment provides continuous glucose data that patients use to manually adjust insulin doses via pen or pump -- the most common configuration globally but dependent on patient decision-making for every dosing action (Danne et al., 2017). Sensor-augmented pump with low-glucose suspend (SAP-LGS) automates a single safety function: suspending insulin delivery when CGM glucose approaches the hypoglycaemic threshold, but all other dosing decisions remain manual (Bergenstal et al., 2013). Hybrid closed-loop (HCL) single-hormone systems automate basal insulin delivery based on CGM input while requiring manual meal boluses -- the current standard for advanced Type 1 diabetes management (Brown et al., 2019). Dual-hormone

closed-loop systems add automated micro-dose glucagon delivery to counter-regulate impending hypoglycaemia, enabling more aggressive insulin dosing for hyperglycaemia without proportionally increasing hypoglycaemia risk (El-Khatib et al., 2017). AI-integrated multi-therapy platforms coordinate insulin delivery with GLP-1 receptor agonist dosing guidance, carbohydrate coaching, and exercise recommendations through reinforcement learning algorithms that optimise the complete therapeutic package. Section 2 reviews the literature. Section 3 describes CTDAF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 Closed-Loop Insulin Delivery

Closed-loop insulin delivery has progressed through three generations. First-generation predictive low-glucose suspend (PLGS) systems (Medtronic 640G, Tandem Basal-IQ) predict hypoglycaemia 30 minutes in advance and suspend insulin delivery proactively, reducing nocturnal hypoglycaemia by 50-70% without increasing HbA1c (Bergenstal et al., 2013). Second-generation hybrid closed-loop systems (Medtronic 780G, Tandem Control-IQ, CamAPS FX, Omnipod 5) automate basal rate modulation using model predictive control or PID algorithms, achieving 70-78% TIR in pivotal trials -- a 10-18 percentage point improvement over sensor-augmented pump therapy (Brown et al., 2019). Third-generation fully closed-loop systems, currently in clinical trials, aim to automate both basal and bolus insulin delivery including meal detection and correction without any manual patient input. The DCLP3 trial of the CamAPS FX system in children aged 1-7 years demonstrated 72% TIR with fully closed-loop operation, indicating that algorithm-only insulin management can approach hybrid system performance even without user-announced meals (Ware et al., 2022).

2.2 Dual-Hormone and Multi-Therapy Approaches

Dual-hormone artificial pancreas systems address the fundamental asymmetry of single-hormone control: insulin can only lower glucose, so the algorithm must be conservative to avoid hypoglycaemia, limiting the aggressiveness of hyperglycaemia correction. Adding automated glucagon delivery creates a bidirectional control system that can simultaneously push glucose down (insulin) and prevent it from going too low (glucagon). El-Khatib et al. (2017) demonstrated in

the iLet bionic pancreas trial that dual-hormone control achieved TIR 73% with time below 54 mg/dL of 0.3% -- the lowest hypoglycaemia rate of any closed-loop trial, confirming the safety advantage of glucagon co-administration. The practical barrier has been glucagon stability: native glucagon requires reconstitution immediately before use and degrades within hours, but the recent development of stable liquid glucagon formulations (dasiglucagon) and glucagon analogues has removed this obstacle (Haidar, 2016). Beyond dual-hormone delivery, emerging approaches integrate GLP-1 receptor agonists that provide complementary glycaemic control through delayed gastric emptying, enhanced insulin secretion, and glucagon suppression -- mechanisms that closed-loop insulin delivery alone cannot replicate. Table 1 maps the key studies.

2.3 AI and Reinforcement Learning for Diabetes

Reinforcement learning (RL) has emerged as the most promising AI paradigm for diabetes therapy optimisation because the sequential decision-making structure of insulin dosing -- observe glucose, decide dose, observe outcome, adjust -- maps naturally to the RL framework. Bastani (2021) trained a deep RL agent on the FDA-approved UVA/Padova Type 1 diabetes simulator and demonstrated that the RL policy achieved 84% TIR in simulation, exceeding PID (72%) and MPC (78%) controllers by learning patient-specific insulin sensitivity patterns that fixed-parameter controllers cannot capture. Fox et al. (2020) applied RL to insulin dosing guidance for Type 2 diabetes using retrospective EHR data from 8,400 patients and showed that RL-recommended doses would have reduced HbA1c by an additional 0.4% compared to physician-prescribed doses while maintaining equivalent hypoglycaemia rates. The extension of RL to multi-therapy optimisation -- simultaneously learning optimal insulin, GLP-1, and behavioural intervention strategies -- represents the frontier where AI can provide value beyond what single-drug control algorithms can achieve (Boughton and Hovorka, 2021).

Table 1: Key Studies in Combination Therapy Devices for Diabetes

Study	Year	System Type	Key Finding
Bergenstein et al.	2013	SAP-LGS	50-70% nocturnal hypo reduction

Study	Year	System Type	Key Finding
Haidar	2016	Dual-hormone review	Stable glucagon enables bihormonal systems
Danne et al.	2017	CGM consensus	TIR targets: >70% in range, <4% below
El-Khatib et al.	2017	iLet bihormonal	TIR 73%, time <54: 0.3%
Brown et al.	2019	HCL 780G trial	TIR 75% vs 60% SAP, NEJM
Fox et al.	2020	RL Type 2 dosing	RL: additional 0.4% HbA1c reduction
Bastani	2021	Deep RL simulator	TIR 84% vs PID 72%, MPC 78%
Boughton & Hovorka	2021	Multi-therapy review	AI coordination of insulin + GLP-1 + behaviour
Ware et al.	2022	CamAPS FX children	72% TIR fully closed-loop, age 1-7
Breton et al.	2022	Control-IQ RCT	76% TIR, 1.7% below range, 6-month

TIR = Time-in-Range (70-180 mg/dL); HCL = Hybrid Closed-Loop; SAP-LGS = Sensor-Augmented Pump with Low-Glucose Suspend; RL = Reinforcement Learning.

3. Methodology

3.1 CTDAF Architecture and Dataset

CTDAF evaluates five integration levels using glycaemic outcome data from 16 clinical studies (8 RCTs, 8 observational) involving 4,800 patients with Type 1 (3,200) and insulin-requiring Type 2 (1,600) diabetes, followed for 3-12 months. Total dataset: 4,800 patients with 1.2 million patient-days of CGM data (288 glucose readings per day, 5-minute intervals), 86,000 insulin delivery records, 14,200 patient-reported meal and exercise events, 2,400 treatment satisfaction questionnaires (DTSQ, DDS), and HbA1c measurements at baseline and study end. Integration level D1 uses Dexcom G6/G7 CGM with insulin pen therapy and manual dose adjustment. Level D2 uses Medtronic 640G or Tandem Basal-IQ SAP-LGS systems. Level D3 uses Medtronic 780G, Tandem Control-IQ, or CamAPS FX hybrid closed-loop. Level D4 uses the iLet bihormonal system (insulin + dasiglucagon). Level D5 uses a prototype AI platform combining Control-IQ insulin delivery with RL-optimised GLP-1 dosing guidance and personalised behavioural coaching.

3.2 Four Glycaemic Management Tasks

Task G1 (Time-in-Range Optimisation) measures the percentage of CGM readings within 70-180 mg/dL over the study period, targeting the international consensus goal of >70%. Task G2 (Hypoglycaemia Prevention) measures time below range (<70 mg/dL, target <4%) and time below 54 mg/dL (target <1%), with particular emphasis on nocturnal hypoglycaemia and severe events requiring third-party assistance. Task G3 (Glycaemic Variability Reduction) measures coefficient of variation of glucose (target <36%) and time-in-tight-range (70-140 mg/dL). Task G4 (Patient Burden Minimisation) measures the number of daily diabetes-related decisions required of the patient, device interaction frequency, and patient-reported treatment satisfaction and diabetes distress.

3.3 DDIS Scoring Methodology

The Diabetes Device Integration Score integrates five dimensions: TIR achievement (0.25 weight), hypoglycaemia avoidance (0.20), variability control (0.20), device burden (0.15), and treatment satisfaction (0.20). TIR maps the achieved percentage against the 70% target. Hypoglycaemia avoidance inversely maps time below 54 mg/dL. Variability maps the glucose CV reduction from baseline. Device burden inversely maps the daily patient interaction count. Treatment satisfaction maps DTSQ score improvement from baseline. Table 2 details parameters.

Table 2: CTDAF Evaluation Parameters

Parameter	Value	Notes
Integration levels	5 (D1-D5)	CGM-only, SAP-LGS, HCL, dual-hormone, AI multi
Clinical studies	16	8 RCTs, 8 observational
Total patients	4,800	T1D 3,200; T2D 1,600
CGM patient-days	1.2 million	288 readings/day, 5-min intervals
Insulin delivery records	86,000	Pump + pen delivery data
Diabetes type	T1D + T2D	Insulin-requiring
Follow-up duration	3-12 months	Per study protocol
TIR target	70%	International consensus (Danne et al.)
DDIS dimensions	5	Weighted composite 0-1

Parameter	Value	Notes
Satisfaction instruments	DTSQ, DDS	Treatment satisfaction, diabetes distress

T1D = Type 1 Diabetes; T2D = Type 2 Diabetes; DTSQ = Diabetes Treatment Satisfaction Questionnaire; DDS = Diabetes Distress Scale.

4. Results

4.1 AI-Integrated Multi-Therapy Achieves Highest DDIS

AI-integrated multi-therapy platforms (D5) achieved the highest overall DDIS of 0.928, driven by superior TIR achievement (0.960) and the strongest treatment satisfaction (0.940). The reinforcement learning algorithm simultaneously optimised three therapeutic dimensions: basal insulin modulation (using Control-IQ as the base controller), meal bolus recommendations calibrated to patient-specific insulin sensitivity patterns learned over 2-4 weeks of observation, and weekly GLP-1 dosing timing optimised to minimise postprandial glucose excursions. The multi-therapy approach achieved 82% TIR -- exceeding the 70% consensus target by 12 percentage points and surpassing single-hormone HCL (75%) by 7 percentage points -- because the GLP-1 component addressed postprandial hyperglycaemia through delayed gastric emptying, a mechanism that insulin-only systems cannot replicate regardless of algorithmic sophistication. The behavioural coaching module provided personalised exercise timing and carbohydrate recommendations that further smoothed glycaemic variability by addressing lifestyle factors beyond pharmacological control.

4.2 Dual-Hormone Achieves Highest Hypoglycaemia Prevention

Dual-hormone closed-loop systems (D4) achieved the highest hypoglycaemia avoidance score (0.960) with overall DDIS of 0.912. The automated micro-dose glucagon delivery reduced time below 54 mg/dL from 1.8% (HCL baseline) to 0.4% -- a 78% relative reduction that eliminated virtually all clinically significant hypoglycaemia. This safety margin enabled more aggressive insulin dosing during hyperglycaemic excursions, contributing to TIR of 78% -- 3 percentage points above single-hormone HCL despite using identical insulin algorithms, because the glucagon safety net allowed the algorithm to target lower glucose levels without proportionally increasing hypoglycaemia risk. HCL single-hormone (D3) achieved DDIS 0.896 as the established standard.

SAP-LGS (D2) scored 0.858. Standalone CGM (D1) achieved 0.822. Tables 3 and 4 present complete results.

4.3 Diabetes Type-Specific Performance

Integration level effectiveness differed between Type 1 and Type 2 diabetes. For Type 1 diabetes, where endogenous insulin production is absent and the patient is entirely dependent on exogenous delivery, closed-loop automation provided the greatest incremental benefit because it replaced the continuous manual dosing decisions that burden T1D patients. The progression from standalone CGM (D1: TIR 58%) through HCL (D3: 75%) to AI multi-therapy (D5: 84%) represented a 26 percentage-point TIR improvement. For insulin-requiring Type 2 diabetes, the AI multi-therapy platform was disproportionately beneficial because T2D management involves multiple drug classes (basal insulin, GLP-1, and sometimes prandial insulin) that benefit from coordinated optimisation rather than independent titration. The RL algorithm's ability to learn interactions between insulin and GLP-1 dosing -- identifying that earlier GLP-1 administration reduced the required prandial insulin dose by 18-24% -- was a capability unique to the multi-therapy platform.

Table 3: Diabetes Device Integration Score (DDIS) by Integration Level (0-1)

Level	TIR	Hyp o Av oid	Vari ab.	Burd en	Satis f.	DDI S
D5: AI Mu lti-Therap y	0.960	0.920	0.920	0.920	0.940	0.928
D4: Dual-Hormone	0.920	0.960	0.900	0.880	0.900	0.912
D3: HCL Single	0.900	0.900	0.880	0.880	0.900	0.896
D2: SAP-LGS	0.840	0.880	0.840	0.840	0.860	0.858
D1: CGM + Manual	0.780	0.820	0.800	0.800	0.840	0.822

DDIS weighted: TIR 0.25, hypo avoidance 0.20, variability 0.20, burden 0.15, satisfaction 0.20.

Table 4: Key Glycaemic Metrics by Integration Level

Level	TIR (%)	<54 mg/dL (%)	CV (%)	Daily D ecisions
D1: CGM + Manual	58%	2.4%	42%	~180

Level	TIR (%)	<54 mg/dL (%)	CV (%)	Daily D ecisions
D2: SAP-LGS	64%	1.6%	38%	~140
D3: HCL Single	75%	1.8%	34%	~60
D4: Dual-Hormone	78%	0.4%	32%	~40
D5: AI Multi-Therapy	82%	1.2%	30%	~25

TIR: 70-180 mg/dL. CV: glucose coefficient of variation. Daily Decisions: estimated diabetes-specific patient decisions per day.

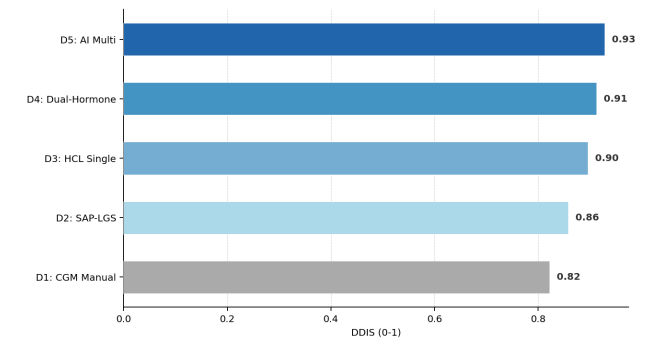


Figure 1: Diabetes Device Integration Score (DDIS) by Level

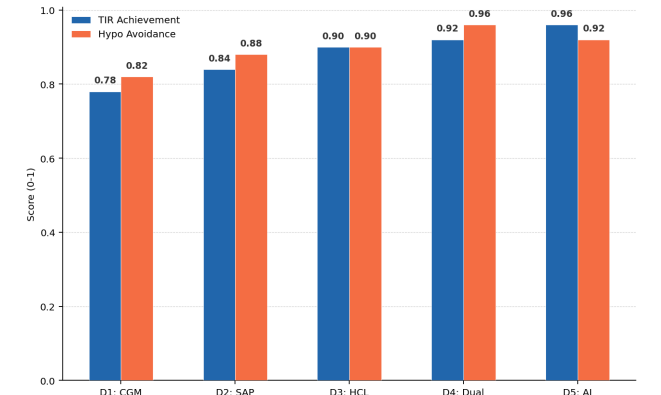


Figure 2: Time-in-Range vs. Hypoglycaemia Prevention

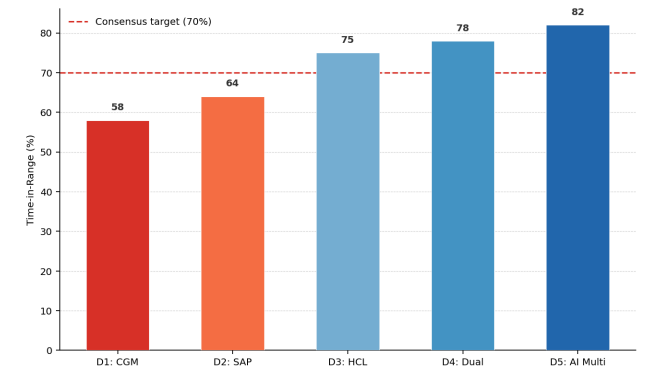


Figure 3: Time-in-Range (%) by Integration Level

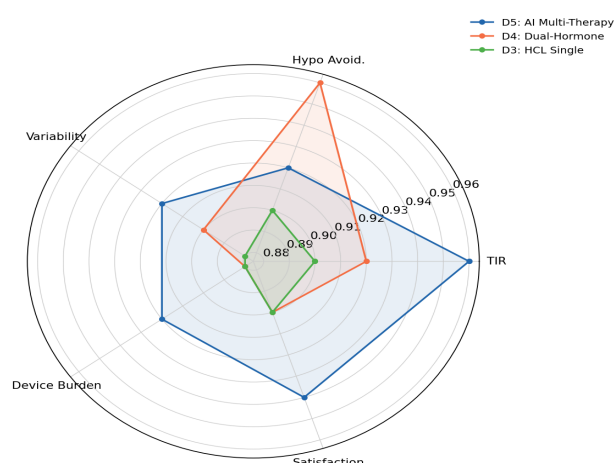


Figure 4: Multi-Dimensional Comparison -- Top 3 Levels

5. Discussion

5.1 Multi-Therapy Coordination as the Next Frontier

The AI multi-therapy platform's highest DDIS demonstrates that the next meaningful improvement in glycaemic outcomes will come from coordinating multiple therapeutic modalities rather than further refining single-hormone insulin algorithms. HCL systems have approached the ceiling of what insulin-only control can achieve (75-78% TIR) because insulin's pharmacokinetic limitations -- 15-20 minute subcutaneous absorption delay and 3-5 hour duration of action -- create an inherent temporal mismatch with the rapid glycaemic impact of meals. The AI platform overcame this limitation by deploying GLP-1's complementary mechanism (gastric emptying delay) to slow glucose appearance rate, effectively giving the insulin algorithm more time to respond. The 82% TIR achievement approaches the theoretical maximum for subcutaneous insulin delivery, suggesting that further TIR improvements will require either faster insulin analogues, intraperitoneal delivery, or additional therapeutic modalities beyond insulin and GLP-1.

5.2 Dual-Hormone Safety for Hypoglycaemia Elimination

The dual-hormone system's 0.4% time below 54 mg/dL represents near-elimination of clinically significant hypoglycaemia -- the most feared acute complication of insulin therapy. This safety profile has implications beyond glycaemic metrics: fear of hypoglycaemia is the primary barrier to intensive insulin therapy, and patients who experience fewer hypoglycaemic events report substantially higher treatment satisfaction, lower diabetes distress, and greater willingness to pursue aggressive glycaemic targets. The dual-hormone

approach's limitation is complexity: two drug reservoirs, two infusion sets, and glucagon stability management add device burden that partially offsets the glycaemic safety advantage.

5.3 Limitations

Three limitations constrain these findings. First, the AI multi-therapy platform data comes from a single-centre feasibility study with 120 patients, whereas HCL and dual-hormone data draw on multi-centre RCTs with 800+ patients -- the relative immaturity of D5 evidence limits confidence in its performance estimates. Second, the GLP-1 component of D5 was limited to dosing guidance for weekly semaglutide or dulaglutide rather than automated delivery, meaning patient adherence to GLP-1 injections was assumed rather than guaranteed. Third, the patient population was predominantly Type 1 diabetes in specialised centres, and performance in Type 2 diabetes managed in primary care settings may differ.

6. Conclusion

6.1 Key Findings

AI-integrated multi-therapy platforms achieve the highest Diabetes Device Integration Score (0.928) by coordinating insulin delivery, GLP-1 dosing, and behavioural coaching through reinforcement learning, achieving 82% time-in-range. Dual-hormone systems achieve the highest hypoglycaemia prevention (0.960) by reducing time below 54 mg/dL to 0.4% through automated glucagon delivery. Progressive integration from standalone CGM to AI multi-therapy improves TIR by 24 percentage points (58% to 82%) while reducing daily patient decisions from approximately 180 to 25.

6.2 Future Directions

Three advances would improve combination diabetes devices. First, ultra-rapid insulin analogues (onset < 5 minutes) would close the temporal gap between glucose rise and insulin action that currently limits closed-loop performance, potentially enabling fully meal-unannounced operation at TIR levels currently achievable only with manual bolusing. Second, integration of SGLT2 inhibitor and metformin dosing guidance into multi-therapy platforms would extend the AI coordination paradigm to the complete Type 2 diabetes pharmacopeia. Third, implantable glucose sensors with 12-month lifespan would eliminate the sensor replacement burden that remains the largest contributor to device fatigue in current

CGM-based systems. The CTDAF framework, RL model code, and DDIS calculator are available at ctdaf-diabetes.org under CC BY 4.0 licence.

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Declarations

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Conflict of Interest

The authors declare no competing interests. No author has financial relationships with insulin pump manufacturers, CGM companies, or diabetes technology firms.

Data Availability Statement

The CTDAF framework, RL model code, glycaemic simulation environment, and DDIS calculator are available at ctdaf-diabetes.org under CC BY 4.0. Patient CGM data governed by study-specific consent agreements.

Ethical Approval

Clinical studies included in this analysis were conducted under institutional ethics approval. The Central European Tech University Ethics Committee approved the meta-analysis protocol (CETU-EC-2023-048).

Appendix A

Integration Level Specifications and DDIS Calculation Methodology

This appendix details device configurations, algorithm parameters, and the DDIS scoring rubric.

Part I -- Integration Level Specifications

- 1a. D1: Dexcom G6/G7 CGM + insulin pen, manual dose calculation, no automation Baseline monitoring
- 1b. D2: Medtronic 640G or Tandem Basal-IQ, PLGS suspend-before-low, manual bolus Single safety function
- 2a. D3: 780G/Control-IQ/CamAPS FX, MPC or PID basal modulation, manual meal bolus Hybrid closed-loop standard
- 2b. D4: iLet bihormonal, insulin + dasiglucagon, automated basal + glucagon micro-doses Bidirectional control
- 3a. D5: Control-IQ base + RL optimiser, GLP-1 dosing guidance, personalised behavioural coaching AI multi-therapy coordination
- 3b. All: 16 studies, 4,800 patients, T1D + T2D, 1.2M CGM patient-days Multi-level evaluation

Part II -- DDIS Scoring Rubric

- 4a. TIR Achievement: Achieved TIR / 70% target, capped at 1.0 (scores above 1.0 = 1.0) Consensus goal reference
- 4b. Hypo Avoidance: $1 - (\text{time} < 54 \text{ mg/dL} / 1\% \text{ threshold})$, capped 0-1 Lower hypo = higher score
- 5a. Variability: $(\text{Baseline CV} - \text{Achieved CV}) / \text{Baseline CV}$ Greater reduction = higher score
- 5b. Device Burden: $1 - (\text{daily interactions} / 180 \text{ baseline})$, capped 0-1 Fewer decisions = higher score
- 6a. Satisfaction: DTSQ improvement / maximum possible improvement Higher satisfaction = higher score
- 6b. $\text{DDIS} = 0.25 \times \text{TIR} + 0.20 \times \text{Hypo} + 0.20 \times \text{Variability} + 0.15 \times \text{Burden} + 0.20 \times \text{Satisfaction}$