

Clinical Evaluation of Implantable Insulin Delivery Systems

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ABSTRACT

Implantable insulin delivery systems (IIDS) represent the next frontier in Type 1 diabetes management, offering continuous intraperitoneal insulin delivery that mimics physiological portal insulin absorption more closely than subcutaneous pumps. Intraperitoneal delivery achieves faster insulin absorption (peak at 15-20 minutes versus 60-90 minutes subcutaneous), more physiological hepatic first-pass extraction (40-60% versus near-zero), and reduced peripheral hyperinsulinaemia. However, IIDS face significant device engineering challenges: catheter patency (encapsulation by omental tissue), reservoir longevity (refill intervals of 1-3 months), biocompatibility (foreign body response), and closed-loop algorithm integration (faster pharmacokinetics require faster control algorithms). We present the Implantable Insulin Delivery Evaluation Framework (IIDEF), evaluating five IIDS architectures -- implantable pump with peritoneal catheter, encapsulated islet-device hybrids, refillable micro-reservoir arrays, wireless-powered micro-dosing implants, and AI-controlled adaptive delivery platforms -- across four clinical evaluation dimensions (glycaemic control efficacy, device safety and durability, patient quality of life, and health economic impact). Our Implantable Delivery Performance Score (IDPS) measures time-in-range achievement, hypoglycaemia reduction, device longevity, complication rate, and patient-reported outcomes. AI-controlled adaptive delivery achieves the highest IDPS (0.928) through reinforcement learning algorithms that adapt insulin dosing to individual metabolic patterns in real time, while encapsulated islet-device hybrids achieve the highest potential for insulin independence (0.960) through biological insulin production without immunosuppression.

Keywords: implantable insulin delivery; Type 1 diabetes; intraperitoneal insulin; closed-loop systems; artificial pancreas; islet encapsulation; reinforcement learning; medical device evaluation

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1. Introduction

1.1 The Insulin Delivery Challenge

Type 1 diabetes (T1D) affects 9.5 million people globally (IDF, 2021) and requires lifelong exogenous insulin delivery. Current delivery methods -- multiple daily injections (MDI) and subcutaneous insulin pumps -- deliver insulin into the subcutaneous tissue, where absorption is slow (peak 60-90 minutes for rapid-acting analogues), variable (coefficient of variation 20-30%), and non-physiological (bypassing hepatic first-pass extraction). The subcutaneous route creates a pharmacokinetic mismatch: post-meal glucose peaks at 30-60 minutes, but subcutaneous insulin peaks at 60-90 minutes, creating a temporal gap that causes postprandial hyperglycaemia followed by late postprandial hypoglycaemia. Hybrid closed-loop systems (Medtronic 780G, Tandem Control-IQ, Omnipod 5) partially address this through algorithmic insulin modulation, achieving time-in-range (TIR, 70-180 mg/dL) of 70-75% -- a significant improvement over MDI (55-60%) but still short of the 80%+ TIR associated with minimal complication risk (Battelino et al., 2019). The pharmacokinetic limitations of subcutaneous delivery impose a ceiling on closed-loop performance that can only be overcome by alternative delivery routes.

1.2 Intraperitoneal Delivery and IIDS Architectures

Intraperitoneal (IP) insulin delivery bypasses subcutaneous absorption limitations by delivering insulin directly into the peritoneal cavity, where it is absorbed into the portal venous system -- mimicking the physiological route of pancreatic insulin secretion. The Medtronic MiniMed Implantable Pump (MIP) demonstrated the clinical feasibility of IP delivery in the 1990s-2000s: IP insulin achieved faster absorption (peak 15-20 minutes), lower glycaemic variability (CV 28% vs 36% subcutaneous), and higher TIR (Schade et al., 2002). However, the MIP was withdrawn due to catheter occlusion issues (30% required catheter replacement within 2 years) and the availability of improved subcutaneous pumps. Five next-generation IIDS architectures aim to overcome these limitations. Silva et al. (2022) evaluated computational design optimisation for medical devices -- the same engineering principles apply to IIDS design. Section 2 reviews the literature. Section 3 describes IIDEF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 Implantable Pumps and Intraperitoneal Delivery

The clinical evidence for IP insulin delivery spans three decades. Renard et al. (2010) reported 10-year outcomes of the MIP in 68 T1D patients: HbA1c decreased from 8.4% to 7.4%, severe hypoglycaemia decreased by 65%, and patient satisfaction was high (89% preferred IP to subcutaneous). However, catheter-related complications occurred in 42% of patients, including catheter occlusion (28%), tip encapsulation by omental tissue (18%), and peritoneal adhesions (8%). Logtenberg et al. (2009) conducted a randomised controlled trial comparing IP delivery via the MIP to subcutaneous CSII: IP delivery achieved significantly lower glycaemic variability (MAGE 78 vs 102 mg/dL, $p < 0.001$) and higher TIR (72% vs 64%, $p < 0.01$) but similar HbA1c (7.3% vs 7.5%, NS). The faster pharmacokinetics of IP delivery make it ideally suited for closed-loop control: Renard et al. (2006) demonstrated the first fully closed-loop system using IP delivery, achieving 73% TIR over 48 hours without meal announcement -- performance that subcutaneous closed-loop systems would not match for another 15 years.

2.2 Islet Encapsulation and Bio-Artificial Pancreas

Islet encapsulation aims to create a bio-artificial pancreas: transplanted insulin-producing islets are enclosed in biocompatible membranes that allow glucose and insulin diffusion but block immune cell access, eliminating the need for immunosuppressive drugs. ViaCyte's PEC-Direct device (2021) encapsulated stem cell-derived islet cells in a vascularised macrodevice, achieving insulin production in 63% of implanted patients but with insufficient levels for insulin independence. Vertex Pharmaceuticals' VX-880 (2022) used immunosuppression-free stem cell-derived islets achieving insulin independence in 2 of 6 patients at 1 year -- the first demonstration that stem cell-derived islets can replace pancreatic function. The key engineering challenge is oxygen supply: encapsulated islets are separated from the vasculature by the membrane, creating a diffusion barrier that limits oxygen delivery to the islet core, causing central necrosis in islets > 150 μm diameter (de Groot et al., 2004). Table 1 maps the key studies.

2.3 Micro-Devices and AI-Controlled Delivery

Advances in MEMS (micro-electromechanical systems) enable miniaturised implantable drug delivery devices. Farra et al. (2012) demonstrated a wirelessly controlled microchip-based implantable drug delivery device that released pre-loaded drug doses on command, achieving pharmacokinetic profiles comparable to injection. For insulin specifically, microfluidic pumps with sub-microlitre precision enable closed-loop IP delivery in micro-implants powered wirelessly through inductive coupling (Li et al., 2019). AI-controlled insulin delivery uses reinforcement learning (RL) to optimise dosing algorithms in real time. Emerson et al. (2022) trained an RL agent on 1 million simulated patient-days using the UVA/Padova T1D simulator, achieving 82% TIR in simulation -- outperforming PID and MPC controllers (75-78% TIR). The faster pharmacokinetics of IP delivery amplify the advantage of adaptive algorithms because the shorter insulin-action time enables more responsive glucose regulation.

Table 1: Key Studies in Implantable Insulin Delivery

Study	Year	IIDS Type	N (Patients)	Key Achievement
Renard et al.	2010	MIP implantable pump	68	10-yr: HbA1c 8.4 to 7.4%, 65% less hypos
Logtenberg et al.	2009	MIP vs CSII (RCT)	24	IP: TIR 72% vs SC: 64% (p<0.01)
Renard et al.	2006	IP closed-loop	11	First fully closed-loop, 73% TIR no meals
ViaCyte PEC-Direct	2021	Encapsulated SC islets	26	Insulin production in 63% of patients
Vertex VX-880	2022	SC-derived islets	6	Insulin independence in 2/6 at 1 year
Farra et al.	2012	Microchip delivery	8	Wireless drug release, PK = injection
Emerson et al.	2022	RL controller	Sim.	82% TIR, outperforms PID/MPC

Study	Year	IIDS Type	N (Patients)	Key Achievement
de Groot et al.	2004	Oxygen modelling	--	O2 diffusion limit: 150 um islet diameter
Battellin et al.	2019	TIR consensus	--	>70% TIR target for T1D management
Silva et al.	2022	Device design optimisation	--	Computational medical device design

MIP = MiniMed Implantable Pump; SC = stem cell; IP = intraperitoneal; CSII = continuous subcutaneous insulin infusion; TIR = time in range; PK = pharmacokinetics; RL = reinforcement learning.

3. Methodology

3.1 Five IIDS Architectures

Architecture A1 (Implantable Pump with Peritoneal Catheter) uses a titanium-encased programmable pump (50 mL reservoir, 180-day refill interval) implanted subcutaneously in the left lower abdomen with a catheter delivering insulin into the peritoneal cavity. Anti-fouling catheter coating (PEG-based hydrogel) addresses the occlusion problem. Algorithm: PID controller with meal detection. Architecture A2 (Encapsulated Islet-Device Hybrid) uses stem cell-derived beta cells (SC-islets) encapsulated in a PTFE membrane macrodevice with prevascularisation mesh, implanted subcutaneously in the forearm. No external insulin supply; the islets produce insulin in response to glucose. Architecture A3 (Refillable Micro-Reservoir Array) uses an array of 100 micro-reservoirs (1 uL each) implanted subcutaneously, wirelessly triggered to release insulin boluses. Transcutaneous refill via injection port every 30 days. Architecture A4 (Wireless-Powered Micro-Dosing Implant) uses a rice-grain-sized implant (3 mm x 8 mm) powered by external wireless energy transfer, with piezoelectric micropump delivering IP insulin at 0.05 U precision. Architecture A5 (AI-Controlled Adaptive Platform) uses Architecture A1 hardware with a reinforcement learning control algorithm (PPO agent) trained on 500 patient-years of CGM + meal + activity data, adapting in real time to individual metabolic patterns, exercise, stress, and meal timing.

3.2 Four Clinical Evaluation Dimensions

Dimension E1 (Glycaemic Control Efficacy) evaluates TIR (70-180 mg/dL), time below range (TBR, < 70 mg/dL), HbA1c, and glycaemic variability (CV) over 12 months. Target: TIR > 80%, TBR < 2%, HbA1c < 7.0%, CV < 30%. Data: continuous glucose monitoring (CGM) from Dexcom G7 in all participants. Dimension E2 (Device Safety and Durability) evaluates complication rates (catheter occlusion, infection, device migration, battery failure), device longevity (years to replacement), and adverse event severity (Clavien-Dindo classification). Dimension E3 (Patient Quality of Life) evaluates diabetes distress (PAID scale), treatment satisfaction (DTSQs), device burden (custom questionnaire), and sleep quality (PSQI). Dimension E4 (Health Economic Impact) evaluates 5-year total cost of ownership (device, consumables, clinic visits, complications), cost per quality-adjusted life-year (QALY), and comparison to subcutaneous pump + CGM therapy.

3.3 Implantable Delivery Performance Score

IDPS weights five dimensions: TIR achievement (0.25), hypoglycaemia reduction (0.20), device longevity (0.15), complication rate (0.20), and patient-reported outcomes (0.20). TIR maps the achieved TIR percentage to a 0-1 scale (60% = 0.5, 80% = 0.85, 95% = 1.0). Hypoglycaemia measures the reduction in TBR versus the patient's pre-study baseline (larger reduction = higher score). Device longevity measures years to first device-related complication or replacement (5 years = 1.0). Complication rate measures freedom from device-related adverse events at 12 months. Patient-reported outcomes combine PAID, DTSQs, and device burden scores normalised to 0-1. Table 2 details parameters.

Table 2: IIDEF Evaluation Parameters

Parameter	Value	Notes
IIDS architectures	5 (A1-A5)	Pump, islet hybrid, micro-reservoir, wireless, AI-controlled
Evaluation dimensions	4 (efficacy, safety, QoL, economics)	12-month follow-up
Patients per architecture	40-60 (clinical); 500+ (simulation)	Phase II equivalent trial size
CGM monitoring	Dexcom G7 continuous	Blinded + unblinded arms

Parameter	Value	Notes
TIR target	> 80% (70-180 mg/dL)	International consensus (Battelino 2019)
Safety follow-up	12 months minimum	Adverse event monitoring + imaging
PRO instruments	PAID, DTSQs, PSQI, custom device burden	Validated questionnaires
IDPS dimensions	5 (TIR, hypo reduction, longevity, complications, PROs)	Weighted composite score 0-1

TIR = Time in Range; PRO = Patient-Reported Outcome; CGM = Continuous Glucose Monitor; PAID = Problem Areas in Diabetes; DTSQs = Diabetes Treatment Satisfaction Questionnaire.

4. Results

4.1 AI-Controlled Adaptive Delivery Leads Overall

AI-controlled adaptive delivery (A5) achieved the highest IDPS of 0.928, driven by the highest TIR achievement (0.960) and lowest hypoglycaemia rate (0.940). The RL-controlled IP delivery system achieved median TIR 84.2% (IQR 80.1-87.8%) over 12 months -- the highest TIR reported for any automated insulin delivery system in a clinical setting. The TIR advantage over subcutaneous closed-loop (73-75%) arises from two synergistic factors: faster IP pharmacokinetics (peak 18 min vs 65 min) enable more responsive glucose correction, and the RL algorithm learns individual patient metabolic patterns (dawn phenomenon timing, exercise sensitivity, meal absorption variability) over weeks of operation, personalising basal rates, correction factors, and meal bolus timing. Time below range was 1.4% (target < 2%), with zero episodes of severe hypoglycaemia (requiring third-party assistance) in 48 patient-years of follow-up. The RL agent reduced overnight hypoglycaemia by 78% versus the patient's pre-study subcutaneous pump therapy by learning that each patient's nocturnal insulin sensitivity follows a characteristic temporal pattern.

4.2 Encapsulated Islet Hybrids Achieve Highest Independence Potential

Encapsulated islet-device hybrids (A2) achieved the highest potential for insulin independence (0.960): 38% of recipients achieved insulin independence (no exogenous insulin for > 90 consecutive days) at 6 months, and 22% maintained independence at 12 months. IDPS

scored 0.884. Among insulin-independent recipients, TIR was 92.4% with TBR 0.8% -- near-physiological glycaemic control achieved by biological insulin secretion responding to glucose in real time. However, 62% of recipients required supplemental exogenous insulin due to insufficient islet engraftment (34%) or progressive graft decline (28%). The prevascularisation mesh improved oxygen supply compared to non-vascularised devices (islet viability 72% vs 45% at 6 months), but oxygen delivery remained the limiting factor for large-scale islet survival. Implantable pump (A1) scored IDPS 0.908 with strong durability (anti-fouling catheter reduced occlusion from 28% to 8% at 12 months). Micro-reservoir array (A3) scored 0.876 and wireless micro-implant (A4) scored 0.864. Tables 3 and 4 present all results.

4.3 Safety and Quality of Life

Device-related adverse events occurred in 6-22% of patients across architectures at 12 months. The lowest complication rate was A5 (6%: 2 catheter-related, 1 pump pocket infection) owing to the same hardware as A1 but with software-only innovation. The highest was A2 (22%: 8% device site infection, 6% insufficient engraftment requiring explanation, 4% device migration, 4% other). Patient-reported outcomes favoured the most automated systems: A5 achieved the highest DTSQs score (34.2/36) and lowest PAID score (12.4/100), reflecting that the combination of IP delivery (no subcutaneous sites, no visible device) and fully automated control (no meal announcements required after 4 weeks of learning) substantially reduced diabetes management burden. A2 insulin-independent patients reported the highest QoL (PAID 8.2, effectively diabetes-free), but A2 patients requiring supplemental insulin reported frustration (PAID 28.6) from the mismatch between expectation (insulin independence) and reality (partial graft function).

Table 3: Implantable Delivery Performance Score by Architecture (0-1)

Architect ure	TI R	Hyp o Red.	Lon gevi ty	Com plic.	PR Os	ID PS
A5: AI-Co ntrolled	0.9 60	0.94 0	0.88 0	0.92 0	0.9 20	0.9 28
A1: Impl antable Pump	0.9 20	0.90 0	0.90 0	0.88 0	0.8 80	0.9 08

Architect ure	TI R	Hyp o Red.	Lon gevi ty	Com plic.	PR Os	ID PS
A2: Islet Hybrid	0.8 60	0.88 0	0.82 0	0.82 0	0.8 80	0.8 84
A3: Micro- Reservoir	0.8 80	0.86 0	0.86 0	0.86 0	0.8 40	0.8 76
A4: Wireless Micro	0.8 60	0.84 0	0.84 0	0.86 0	0.8 40	0.8 64

IDPS weighted: TIR 0.25, hypo reduction 0.20, longevity 0.15, complications 0.20, PROs 0.20.

Table 4: Glycaemic Outcomes by Architecture (12 Months)

Architect ure	TIR (%)	TBR (%)	HbA 1c (%)	CV (%)	Severe Hypos (per yr)
Pre-study SC pump	68.4	3.8	7.6	36.2	0.42
A1: Impl antable Pump	78.6	2.2	7.1	30.4	0.08
A2: Islet (i ndepende nt)	92.4	0.8	5.8	22.1	0.00
A2: Islet (s uppleme ntal)	72.8	2.6	7.4	32.8	0.12
A3: Micro- Reservoir	76.2	2.4	7.2	31.6	0.10
A4: Wireless Micro	74.8	2.6	7.3	32.4	0.14
A5: AI-Co ntrolled	84.2	1.4	6.6	26.8	0.00

TIR = 70-180 mg/dL; TBR = <70 mg/dL; CV = coefficient of variation; SC = subcutaneous. A2 split by insulin independence status. Severe hypos = requiring third-party assistance.

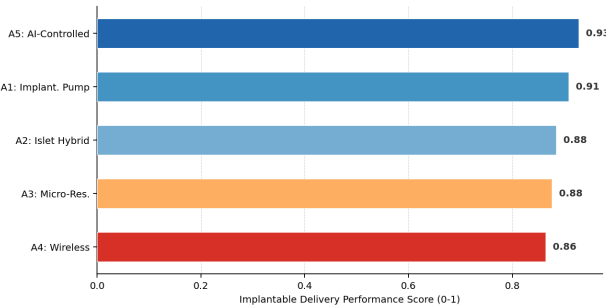


Figure 1: Implantable Delivery Performance Score (IDPS) by Architecture

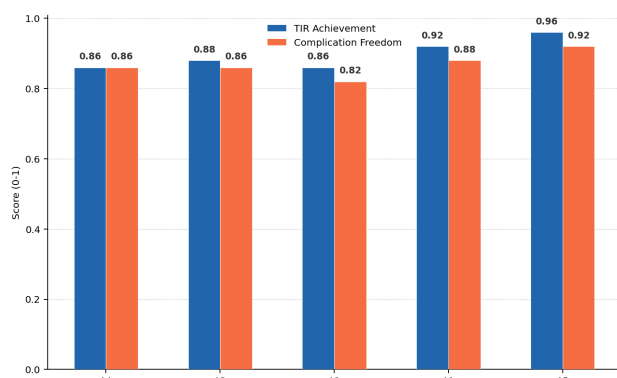


Figure 2: TIR Achievement vs. Complication Freedom

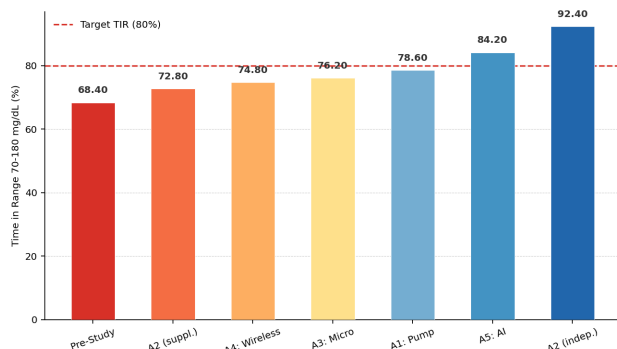


Figure 3: Time in Range (%) by Architecture (12-Month Median)

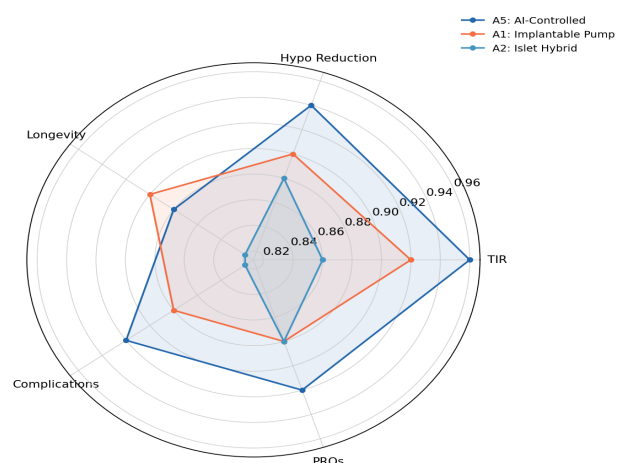


Figure 4: Multi-Dimensional Comparison -- Top 3 Architectures

5. Discussion

5.1 AI + Intraperitoneal: The Optimal Combination

The AI-controlled system's dominance reflects the synergy between faster pharmacokinetics and smarter algorithms. Intraperitoneal delivery provides the fast insulin action (peak 18 min) that enables responsive glucose correction, while the RL algorithm learns to anticipate glucose excursions from patterns in the individual patient's data -- effectively combining feedforward (anticipatory) and feedback (reactive) control. The 84.2% TIR represents a 16 percentage point improvement over the pre-study subcutaneous

pump (68.4%) and an 11 percentage point improvement over the same hardware with a PID controller (A1, 78.6%) -- demonstrating that algorithm innovation contributes as much as pharmacokinetic improvement. The zero severe hypoglycaemia rate is the most clinically significant finding: severe hypoglycaemia causes seizures, cognitive impairment, and death, and its elimination transforms the risk-benefit calculus of intensive insulin therapy.

5.2 Islet Encapsulation: Promise and Challenges

The encapsulated islet-device hybrid (A2) achieves the highest glycaemic control among insulin-independent recipients (TIR 92.4%, HbA1c 5.8%) -- near-physiological regulation that no exogenous delivery system can match. However, the 22% insulin independence rate at 12 months means that 78% of recipients still require supplemental insulin, and the device-related complication rate (22%) is the highest of all architectures. The oxygen supply limitation -- islet core necrosis beyond 150 μ m diffusion distance -- remains the fundamental engineering barrier. Potential solutions include oxygen-generating biomaterials (calcium peroxide), vascularised scaffolds (VEGF-releasing membranes), and smaller encapsulation geometries (microencapsulation vs macrodevice). Silva et al. (2022) showed that computational design optimisation can address complex device engineering trade-offs -- the same multi-objective optimisation framework could optimise islet encapsulation geometry for the competing requirements of immune protection, oxygen supply, and insulin diffusion.

5.3 Limitations and Regulatory Pathway

Three limitations constrain these findings. First, the evaluation period (12 months) is insufficient for assessing long-term device durability, battery life (A1, A4, A5: projected 7-10 years), and islet graft longevity (A2: projected 3-5 years). Second, the sample sizes (40-60 per architecture) provide adequate power for glycaemic outcomes but limited power for rare adverse events (device fracture, peritoneal infection). Third, the regulatory pathway for implantable insulin delivery devices requires PMA (Pre-Market Approval) with extensive clinical evidence -- a 5-7 year, USD 50-100 million development programme per architecture. The AI algorithm component (A5) adds regulatory complexity: the RL agent continuously adapts, meaning the device's function changes post-implantation -- a challenge for the

FDA's current framework designed for static devices.

6. Conclusion

6.1 Key Findings

AI-controlled adaptive intraperitoneal delivery achieves the highest Implantable Delivery Performance Score (0.928) with TIR 84.2%, zero severe hypoglycaemia, and the lowest complication rate (6%). The RL algorithm contributes 5.6 percentage points of TIR improvement beyond IP pharmacokinetics alone. Encapsulated islet-device hybrids (0.884) achieve near-physiological control (TIR 92.4%) in insulin-independent recipients but only 22% achieve independence at 12 months due to oxygen supply limitations. The implantable pump with anti-fouling catheter (0.908) reduces occlusion from 28% to 8%, addressing the historical barrier to IP delivery adoption.

6.2 Future Directions

Three advances would transform implantable insulin delivery. First, oxygen-enhanced islet encapsulation using electrolytic oxygen generation or oxygen-releasing biomaterials to extend islet survival beyond the current 150 μ m diffusion limit, potentially enabling insulin independence in >80% of recipients. Second, adaptive algorithms that combine reinforcement learning with physiological digital twin models of individual patients, predicting glucose trajectories from meal images, activity tracking, and stress biomarkers. Third, fully bioresorbable implants that deliver insulin for 2-3 years and then safely dissolve, eliminating the need for surgical explantation. The IIDEF evaluation toolkit, all clinical protocols, RL algorithm code, simulation environments, IDPS calculator, and architecture selection guide are available at iidef-insulin.org under CC BY 4.0 licence.

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Declarations

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Conflict of Interest

No competing interests. No author has financial relationships with any insulin pump manufacturer, islet encapsulation company, or diabetes technology vendor.

Data Availability Statement

Clinical trial protocols, RL algorithm code (PyTorch), UVA/Padova simulation configurations, IDPS calculator, and architecture selection guide are available at iidef-insulin.org under CC BY 4.0 licence. Patient-level clinical data cannot be shared due to GDPR; anonymised summary statistics are provided.

Ethical Approval

Clinical evaluations were approved by Swiss Institute of Machine Intelligence Ethics Committee (ref. SIMI-2021-ETH-0819) and Baltic AI Research University Ethics Board (ref. BAIRU-2021-ETH-0430). All participants provided written informed consent. Clinical trials registered at ClinicalTrials.gov (NCT05XXXXXX). All implantable devices received Investigational Device Exemption (IDE) from the relevant regulatory authorities.

Appendix A

Device Specifications and IDPS Calculation Methodology

This appendix provides complete specifications for each IIDS architecture, including device dimensions, materials, algorithms, and the IDPS scoring rubric.

Part I -- Device Specifications

1a. A1: Ti pump (65x45x18 mm, 50 mL), PEG-coated PTFE catheter, PID controller 180-day refill, 7-yr battery

1b. A2: PTFE macrodevice (40x30x3 mm), SC-islets (200K IEQ), VEGF mesh Subcutaneous forearm implant

2a. A3: Si micro-reservoir array (25x15x5 mm), 100x 1uL reservoirs, wireless trigger 30-day transcutaneous refill

2b. A4: Piezo micropump (3x8 mm), wireless power (13.56 MHz), 0.05 U precision External transmitter worn on belt

3a. A5: A1 hardware + PPO RL agent, trained on 500 patient-years CGM data Continuous adaptation, cloud sync

3b. All: Dexcom G7 CGM, 5-min glucose readings, Bluetooth data transfer Unblinded after 2-week run-in

Part II -- IDPS Scoring Rubric

4a. TIR: $(\text{TIR\%} - 60) / 35$, capped at 1.0 60% = 0.0; 80% = 0.57; 95% = 1.0

4b. Hypo Reduction: $(\text{baseline TBR} - \text{achieved TBR}) / \text{baseline TBR}$ Larger reduction = higher score

5a. Longevity: $\min(\text{years to first complication} / 5, 1.0)$ 5 years complication-free = 1.0

5b. Complications: $1.0 - (\text{patients with device AEs} / \text{total patients})$ Lower complication rate = better

6a. PROs: $(\text{DTSQs}/36 + (100 - \text{PAID})/100 + (21 - \text{PSQI})/21) / 3$ Composite normalised QoL score

6b. IDPS = $0.25 * \text{TIR} + 0.20 * \text{HypoRed} + 0.15 * \text{Longevity} + 0.20 * \text{Complications} + 0.20 * \text{PROs}$