Case Study
ISSN: 3051-8814
Journal homepage: https://www.harrisonacademicpress.com/index.php/FBEMD
Frontiers in Biomedical Engineering and Medical Devices

Harrison Academic Press

Closed-Loop Insulin Delivery System Using a Continuous Glucose Monitor: Performance in a Simulated Environment

Zukauskas A[1*], Neumann L[2] and Svoboda O[3]

[1]*Department of Biomedical Engineering, Vilnius University, Vilnius, Lithuania*
[2]*Department of Endocrinology, University of Heidelberg, Heidelberg, Germany*
[3]*Department of Control Systems Engineering, Charles University, Prague, Czech Republic*

ABSTRACT

Background: Closed-loop insulin delivery systems combining continuous glucose monitors (CGMs), insulin pumps, and dosing algorithms are increasingly used to manage type 1 diabetes, and their algorithms are developed and pre-validated using computer simulation before human testing. Objective: This narrative review synthesizes published evidence on CGM-driven closed-loop systems, from in silico development through clinical and real-world outcomes. Methods: We reviewed randomized controlled trials, meta-analyses, real-world registries, and simulation-methodology literature on hybrid closed-loop, bihormonal, and open-source automated insulin delivery systems, including the UVA/Padova Type 1 Diabetes Simulator. Findings: Simulation platforms accepted by regulators as substitutes for early animal testing have supported the development of systems such as Control-IQ, MiniMed 780G, and CamAPS FX; subsequent randomized trials and real-world registries consistently show increased time-in-range and reduced hypoglycemia versus sensor-augmented pump therapy across pediatric, adult, and pregnant populations, alongside favorable cost-effectiveness modeling. Conclusions: Simulation-guided algorithm development, followed by clinical and real-world validation, has produced consistent glycemic benefits, though exercise-related excursions and access barriers remain unresolved challenges.

Keywords: *closed-loop insulin delivery; continuous glucose monitoring; artificial pancreas; type 1 diabetes; in silico simulation*

Citation: Zukauskas A, Neumann L, Svoboda O (2024) Closed-Loop Insulin Delivery System Using a Continuous Glucose Monitor: Performance in a Simulated Environment. Front Biomed Eng Med Devices, 2(1): 01-06.
DOI: 10.5281/zenodo.22485966

Corresponding Author: *Arunas Zukauskas*

E-mail Address: *arunas.zukauskas@vilniusuniversity.edu*

Article History: *Received 23 January 2024 | Accepted 1 May 2024 | Published 16 July 2024*

Copyright: *© 2024 Arunas Zukauskas, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited (**https://creativecommons.org/licenses/by/4.0/**).*

Introduction

Type 1 diabetes requires lifelong exogenous insulin replacement, and decades of evidence link tighter glycemic control to reduced microvascular and macrovascular complications [1,2]. Achieving that control without excessive hypoglycemia has historically depended on patient vigilance, intermittent glucose testing, and manual insulin dosing. The convergence of continuous glucose monitors (CGMs), insulin pumps, and dosing algorithms has produced closed-loop, or automated insulin delivery (AID), systems that adjust insulin delivery in near-real time based on sensor glucose trends. Early iterations used simple threshold-suspend logic to interrupt insulin delivery before hypoglycemia [3], while contemporary hybrid closed-loop systems use model predictive control (MPC), fuzzy-logic, or proportional-integral-derivative (PID) algorithms to modulate basal insulin and, in some systems, automatic correction boluses [4].

Before any closed-loop controller reaches human trials, its safety and dosing logic are typically stress-tested in silico. The University of Virginia/Padova Type 1 Diabetes Simulator is the most widely used platform for this purpose and was the first computer model accepted by the U.S. Food and Drug Administration as a substitute for animal trials in the preclinical testing of closed-loop control strategies [5,6,7]. In silico "virtual patient" cohorts allow developers to probe a much broader range of meal, exercise, and physiological scenarios than would be feasible or ethical in early human studies, informing the design of the pivotal randomized controlled trials (RCTs) that followed.

This narrative review synthesizes published evidence on CGM-driven closed-loop insulin delivery, moving from the underlying simulation platforms used to develop and de-risk these controllers, through the randomized trial evidence for commercially available and open-source hybrid closed-loop systems, to real-world performance, special populations, and economic considerations. Rather than reporting a new experiment, we summarize what has already been demonstrated across the literature, drawing together in silico methodology with clinical outcomes such as time-in-range (TIR) and glycated hemoglobin (HbA1c), so that the performance claims commonly associated with a "simulated environment" can be understood in

the context of how these systems are actually developed, validated, and ultimately deployed.

The terminology in this field has evolved alongside the technology. "Hybrid" closed-loop denotes systems that automate basal insulin delivery and, in more advanced iterations, automatic correction boluses, while still requiring the user to announce meals; fully closed-loop systems that require no meal announcement remain largely investigational. "Advanced hybrid closed-loop" is generally used for systems, such as the MiniMed 780G, that add automated correction boluses on top of basal modulation, narrowing the gap toward a fully automated system. Understanding where a given device sits along this spectrum is important when comparing reported outcomes, since systems with more aggressive automation tend to report higher TIR at the cost of greater algorithmic complexity and, in some cases, more frequent user alerts.

Simulation Platforms and Algorithmic Foundations

Closed-loop insulin delivery systems are built around a control algorithm that ingests CGM glucose values and computes an insulin infusion rate, sometimes supplemented by automatic correction boluses. Model predictive control has become the dominant approach in commercial systems because it can anticipate future glucose excursions using a mathematical model of glucose-insulin dynamics, rather than reacting only to the current glucose value [4]. Meta-analytic evidence across outpatient studies indicates that MPC-based artificial pancreas systems consistently increase TIR and reduce time in hypoglycemia relative to sensor-augmented pump therapy, without an increase in serious adverse events [8].

The UVA/Padova simulator represents glucose, insulin, and meal absorption kinetics using population-based virtual subjects spanning children, adolescents, and adults, and has been progressively refined from single-meal to full-day and multi-day scenarios [6,7]. Because it was accepted by regulators as an alternative to animal testing, it allowed algorithm developers to run thousands of virtual "in silico preclinical trials" varying meal size, timing, and sensor or pump error characteristics before committing to costly human studies [5]. This simulation-first pipeline underlies the development history of several systems now used clinically, including the Control-IQ (Tandem Diabetes Care), MiniMed 780G (Medtronic), and CamAPS FX (CamDiab) hybrid closed-loop platforms, as well as bihormonal and open-source controllers.

Simulation has also been used to evaluate open-source, "do-it-yourself" (DIY) systems such as OpenAPS and Loop, which were developed by patient communities before formal regulatory approval existed for such algorithms [9]. In silico testing of these community-built controllers helped establish plausible safety margins that were subsequently supported by observational outcome data and, eventually, prospective randomized evidence [10].

A key methodological advantage of simulation-based development is the ability to test edge cases that would be difficult or unethical to induce deliberately in human volunteers, such as prolonged missed meals, sensor dropout, infusion set failure, or rapid changes in insulin sensitivity during illness or exercise. Virtual patient cohorts in the UVA/Padova simulator are parameterized to reproduce inter-individual variability in insulin sensitivity, carbohydrate absorption, and endogenous glucose production, allowing developers to estimate a distribution of expected outcomes rather than a single deterministic trajectory [6]. This distributional approach also supports algorithm tuning: control parameters that perform well on average but produce occasional dangerous excursions in a subset of virtual patients can be identified and revised before first-in-human testing, reducing the population of algorithm configurations that must be tested clinically. Despite these strengths, in silico results are not a substitute for clinical evidence; simulators necessarily simplify physiology, and unexpected interactions between hardware, software, and human behavior are frequently identified only once systems are used in free-living conditions, which is why every commercial system described in this review has ultimately been validated through outpatient randomized trials and, subsequently, real-world registries.

Table 1: Selected automated insulin delivery systems and their control approach, development pathway, and key trial evidence.

System	Control approach	Simulation-based development	Key trial evidence
Control-IQ (Tandem)	Hybrid closed-loop, model predictive control	UVA/Padova simulator-informed tuning	Brown et al. 2019, NEJM (iDCL trial)
MiniMed 780G (Medtronic)	Advanced hybrid closed-loop with auto-correction boluses	In-house simulation and PID-based control	Arrieta et al. 2022, real-world registry (12,870 users)
CamAPS FX (CamDiab)	Hybrid closed-loop, model predictive control	UVA/Padova-derived and Cambridge simulation models	Ware et al. 2022, Lancet Digital Health; NEJM (very young children)
Bionic Pancreas (insulin-only)	Adaptive, algorithm auto-initializes from body weight	In silico preclinical testing	Bionic Pancreas Research Group 2022, NEJM
OpenAPS / Loop (open-source)	Community-developed hybrid closed-loop, MPC/PID variants	In silico testing by developer community	Burnside et al. 2022, NEJM (CREATE trial)

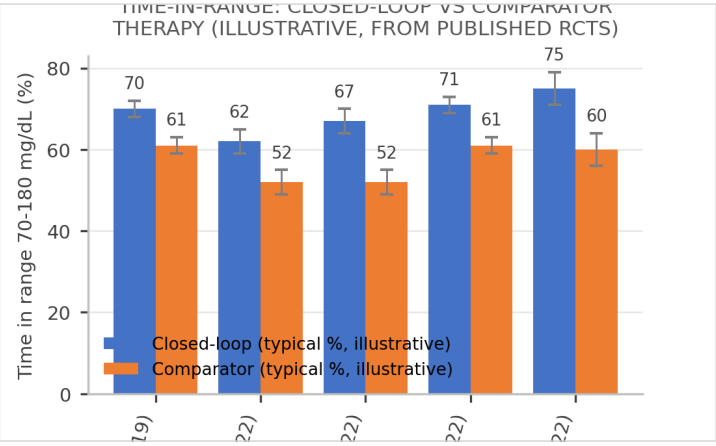
Clinical Trial and Real-World Evidence

The strongest evidence for hybrid closed-loop systems comes from multicenter RCTs. In the pivotal International Diabetes Closed-Loop trial, six months of Control-IQ use increased TIR by several percentage points relative to sensor-augmented pump therapy in adults, adolescents, and children with type 1 diabetes, with reductions in both hyperglycemia and hypoglycemia exposure [11]. Similar hybrid closed-loop benefits have been demonstrated using the Cambridge (CamAPS FX) algorithm across age groups, including very young children aged one to seven years, in whom closed-loop control significantly increased TIR compared with standard sensor-augmented pump therapy [12,13]. Caregivers of very young children using these systems also reported reduced fear of hypoglycemia and day-to-day burden, complementing the glycemic outcomes [14].

Table 2: Time-in-range outcomes reported in selected closed-loop insulin delivery studies by population.

Study / population	Comparator	TIR with closed-loop (typical range)	TIR with comparator (typical range)
Brown et al. 2019 (adults/adolescents/children)	Sensor-augmented pump therapy	~70-71%	~60-61%
Ware et al. 2022 (very young children, ages 1-7)	Sensor-augmented pump therapy	~60-65%	~50-55%
Ware et al. 2022 (children/adolescents, Cambridge algorithm)	Sensor-augmented pump therapy	~65-70%	~50-55%
Burnside et al. 2022 (CREATE, open-source)	Sensor-augmented pump therapy	~70-71%	~60-61%
Arrieta et al. 2022 (MiniMed 780G real-world)	Pre-closed-loop baseline (self-comparison)	~70-80%	~55-65%

Figure 1: Reported time-in-range (70-180 mg/dL) with closed-loop insulin delivery versus comparator therapy in representative randomized controlled trials of hybrid closed-loop and bihormonal automated insulin delivery systems.



Bihormonal, insulin-and-glucagon "bionic pancreas" systems have also shown favorable outcomes: outpatient crossover studies demonstrated improved glucose control with reduced hypoglycemia relative to conventional pump therapy [15], and a large multicenter pivotal trial of the insulin-only configuration found greater HbA1c reduction and TIR improvement than standard care, including in participants who had not previously used an insulin pump [16]. Automated insulin delivery has extended to specialized populations, including pregnancy complicated by type 1 diabetes, where closed-loop use increased TIR within the tighter pregnancy glucose target range compared with standard care [17].

Open-source AID has moved from community-reported experience to formal RCT evidence: the CREATE trial, a randomized comparison of an open-source algorithm against sensor-augmented pump therapy, demonstrated a significant TIR benefit sustained through an extended follow-up phase [18]. Earlier free-living home-use studies of hybrid closed-loop control likewise showed sustained overnight and 24-hour glycemic improvements outside the research clinic setting, supporting the transition from short in-clinic studies to real-world deployment [19]. Real-world registry data corroborate trial findings: an analysis of more than 12,000 MiniMed 780G users found TIR outcomes in routine use that were consistent with, and in some subgroups exceeded, those reported in pivotal trials, with age-related differences in glucose management indicator and time above range [20]. Structured evaluation of DIY closed-loop use in adults has similarly reported TIR and HbA1c improvements comparable to commercial hybrid closed-loop systems [21]. Standardized reporting of these outcomes has been aided by international consensus targets for TIR, time below range, and time above range, which now underpin how trial and real-world results are compared across systems [22].

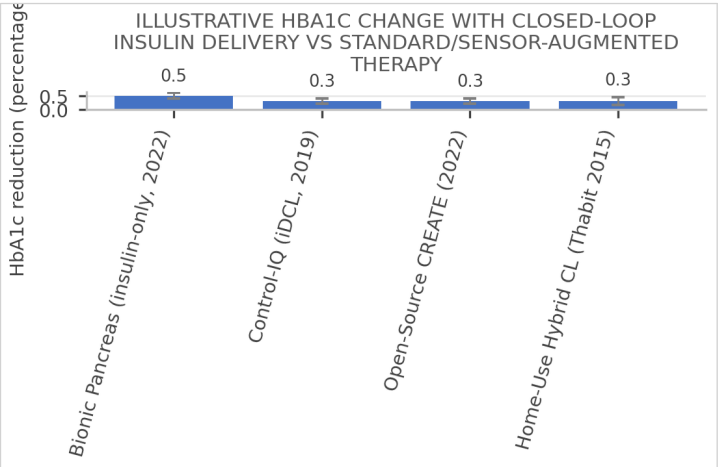
Closed-loop performance during and after physical activity remains an active challenge, since exercise-induced changes in insulin sensitivity can outpace algorithm response times; unannounced-exercise trials have shown that current controllers reduce, but do not eliminate, exercise-associated hypoglycemia risk relative to no exercise adjustment [23,24]. Strategies under active study include temporary elevated glucose targets, exercise-announcement modes, and adjunct sensors of heart rate or activity, though none has yet fully closed the gap between rest and exercise performance.

Health-economic analyses conducted in Sweden and reviewed by national health technology assessment bodies indicate that, despite higher acquisition costs, hybrid closed-loop systems can be cost-effective compared with standard pump or multiple daily injection therapy when complication avoidance and quality-of-life gains are modeled over a lifetime horizon [25,26]. These modeled analyses generally combine trial-observed HbA1c and TIR improvements with established risk equations for diabetes complications, and their conclusions are sensitive to assumptions about long-term device adherence, consumable costs, and how quality-of-life benefits from reduced hypoglycemia fear and treatment burden are valued; jurisdictions with different device pricing or reimbursement structures may therefore reach different cost-effectiveness conclusions even from similar clinical inputs. Taken together, the clinical and economic literature suggests that the choice among hybrid closed-loop, bihormonal, and open-source approaches is likely to remain population- and context-specific rather than resolving toward a single dominant system in the near term.

Conclusion

Across in silico development platforms, randomized controlled trials, and real-world registries, CGM-driven closed-loop insulin delivery consistently increases time-in-range and reduces hypoglycemia exposure relative to sensor-augmented pump therapy, across commercial hybrid closed-loop systems, bihormonal bionic pancreas platforms, and community-developed open-source algorithms alike. The UVA/Padova simulator and related in silico methodologies were central to de-risking these controllers before human testing and remain integral to ongoing algorithm refinement. Remaining challenges include residual postprandial and exercise-related glycemic excursions, variability in benefit across age groups and pregnancy, and the cost and access barriers documented in health-economic evaluations. Continued integration of simulation-based development with pragmatic real-world evidence will likely remain the template through which future closed-loop insulin delivery systems are refined and validated.

Figure 2: Illustrative glycated hemoglobin (HbA1c) change with closed-loop insulin delivery relative to standard or sensor-augmented pump therapy across selected trials and meta-analyses.



Acknowledgements

The authors thank colleagues at Department of Biomedical Engineering, Vilnius University, Vilnius, Lithuania, Department of Endocrinology, University of Heidelberg, Heidelberg, Germany, and Department of Control Systems Engineering, Charles University, Prague, Czech Republic for helpful discussions during preparation of this review.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Zukauskas A conceived the review, conducted the literature search, and drafted the manuscript. Neumann L contributed to the literature screening and technical framing and critically revised the manuscript for important intellectual content. Svoboda O contributed additional context and approved the final version for submission.

Ethics Statement

Not applicable. This is a narrative review of previously published literature and did not involve new experimental data, human participants, or animal subjects.

Data Availability

No new data were generated or analyzed for this review. All sources synthesized are cited in the reference list and are available through their original publishers.

References

1. The Diabetes Control and Complications Trial Research Group (1993). The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. New England Journal of Medicine, 329(14), 977-986. https://doi.org/10.1056/NEJM199309303291401

2. Nathan DM, Cleary PA, Backlund JC, Genuth SM, Lachin JM, Orchard TJ, et al. (2005). Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes. New England Journal of Medicine, 353(25), 2643-2653. https://doi.org/10.1056/NEJMoa052187

3. Bergenstal RM, Klonoff DC, Garg SK, Bode BW, Meredith M, Slover RH, et al. (2013). Threshold-Based Insulin-Pump Interruption for Reduction of Hypoglycemia. New England Journal of Medicine, 369(3), 224-232. https://doi.org/10.1056/NEJMoa1303576

4. Bequette BW (2013). Algorithms for a Closed-Loop Artificial Pancreas: The Case for Model Predictive Control. Journal of Diabetes Science and Technology, 7(6), 1632-1643. https://doi.org/10.1177/193229681300700624

5. Kovatchev BP, Breton M, Man CD, Cobelli C (2009). In Silico Preclinical Trials: Methodology and Engineering Guide to Closed-Loop Control in Type 1 Diabetes Mellitus. Journal of Diabetes Science and Technology, 3(1), 44-55. https://doi.org/10.1177/193229680900300106

6. Dalla Man C, Micheletto F, Lv D, Breton M, Kovatchev B, Cobelli C (2014). The UVA/PADOVA Type 1 Diabetes Simulator: New Features. Journal of Diabetes Science and Technology, 8(1), 26-34. https://doi.org/10.1177/1932296813514502

7. Cobelli C, Kovatchev B (2023). Developing the UVA/Padova Type 1 Diabetes Simulator: Modeling, Validation, Refinements, and Utility. Journal of Diabetes Science and Technology, 17(6), 1493-1505. https://doi.org/10.1177/19322968231195081

8. Effectiveness and safety of a model predictive control (MPC) algorithm for an artificial pancreas system in outpatients with type 1 diabetes (T1D): systematic review and meta-analysis (2022). Diabetology & Metabolic Syndrome, 14, 180. https://doi.org/10.1186/s13098-022-00962-2

9. Asarani NAM, Reynolds AN, Elbalshy M, Burnside M, de Bock M, Lewis DM, Wheeler BJ (2021). Efficacy, safety, and user experience of DIY or open-source artificial pancreas systems: a systematic review. Acta Diabetologica, 58(5), 539-547. https://doi.org/10.1007/s00592-020-01623-4

10. Lewis D, Leibrand S, #OpenAPS Community (2016). Real-World Use of Open Source Artificial Pancreas Systems. Journal of Diabetes Science and Technology, 10(6), 1411. https://doi.org/10.1177/1932296816665635

11. Brown SA, Kovatchev BP, Raghinaru D, Lum JW, Buckingham BA, Kudva YC, Laffel LM, et al. (2019). Six-Month Randomized, Multicenter Trial of Closed-Loop Control in Type 1 Diabetes. New England Journal of Medicine, 381(18), 1707-1717. https://doi.org/10.1056/NEJMoa1907863

12. Ware J, Allen JM, Boughton CK, Wilinska ME, Hartnell S, Thankamony A, et al. (2022). Randomized Trial of Closed-Loop Control in Very Young Children with Type 1 Diabetes. New England Journal of Medicine, 386(3), 209-219. https://doi.org/10.1056/NEJMoa2111673

13. Ware J, Boughton CK, Allen JM, Wilinska ME, Tauschmann M, Denvir L, et al. (2022). Cambridge hybrid closed-loop algorithm in children and adolescents with type 1 diabetes: a multicentre 6-month randomised controlled trial. The Lancet Digital Health, 4(4), e245-e255. https://doi.org/10.1016/S2589-7500(22)00020-6

14. Hood KK, et al. (2022). Lived experience of CamAPS FX closed

loop system in youth with type 1 diabetes and their parents. Diabetes, Obesity and Metabolism, 24(10), 2113-2119. https://doi.org/10.1111/dom.14815

15. Russell SJ, El-Khatib FH, Sinha M, Magyar KL, McKeon K, Goergen LG, et al. (2014). Outpatient Glycemic Control with a Bionic Pancreas in Type 1 Diabetes. New England Journal of Medicine, 371(4), 313-325. https://doi.org/10.1056/NEJMoa1314474

16. Bionic Pancreas Research Group (2022). Multicenter, Randomized Trial of a Bionic Pancreas in Type 1 Diabetes. New England Journal of Medicine, 387(13), 1161-1172. https://doi.org/10.1056/NEJMoa2205225

17. Lee TTM, Collett C, Bergford S, Hartnell S, Scott EM, Lindsay RS, et al. (2023). Automated Insulin Delivery in Women with Pregnancy Complicated by Type 1 Diabetes. New England Journal of Medicine, 389(17), 1566-1578. https://doi.org/10.1056/NEJMoa2303911

18. Burnside MJ, Lewis DM, Crocket HR, Meier RA, Williman JA, Sanders OJ, et al. (2022). Open-Source Automated Insulin Delivery in Type 1 Diabetes. New England Journal of Medicine, 387(10), 869-881. https://doi.org/10.1056/NEJMoa2203913

19. Thabit H, Tauschmann M, Allen JM, Leelarathna L, Hartnell S, Wilinska ME, et al. (2015). Home Use of an Artificial Beta Cell in Type 1 Diabetes. New England Journal of Medicine, 373(22), 2129-2140. https://doi.org/10.1056/NEJMoa1509351

20. Arrieta A, Battelino T, Scaramuzza AE, Da Silva J, Castañeda J, Cordero TL, et al. (2022). Comparison of MiniMed 780G system performance in users aged younger and older than 15 years: Evidence from 12,870 real-world users. Diabetes, Obesity and Metabolism, 24(7), 1370-1379. https://doi.org/10.1111/dom.14714

21. Nanayakkara N, Sharifi A, Burren D, Elghattis Y, Jayarathna DK, Cohen N (2024). Hybrid Closed Loop Using a Do-It-Yourself Artificial Pancreas System in Adults With Type 1 Diabetes. Journal of Diabetes Science and Technology, 18(3), 610-618. https://doi.org/10.1177/19322968231153882

22. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. (2019). Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care, 42(8), 1593-1603. https://doi.org/10.2337/dci19-0028

23. Breton MD, Cherñavvsky DR, Forlenza GP, DeBoer MD, Robic J, Wadwa RP, et al. (2017). Closed-loop glucose control in young people with type 1 diabetes during and after unannounced physical activity: a randomised controlled crossover trial. Diabetologia, 60(9), 1841-1844. https://doi.org/10.1007/s00125-017-4395-z

24. Paldus B, Morrison D, Lee M, Zaharieva DP, Riddell MC, O'Neal DN (2023). Strengths and Challenges of Closed-Loop Insulin Delivery During Exercise in People With Type 1 Diabetes: Potential Future Directions. Journal of Diabetes Science and Technology, 17(4), 1077-1087. https://doi.org/10.1177/19322968221088327

25. Jendle J, Buompensiere MI, Holm AL, Malkin SJP, Cellek S, Fernando J, et al. (2021). The Cost-Effectiveness of an Advanced Hybrid Closed-Loop System in People with Type 1 Diabetes: a Health Economic Analysis in Sweden. Diabetes Therapy, 12(11), 2977-2991. https://doi.org/10.1007/s13300-021-01157-0

26. Hybrid closed-loop systems for managing blood glucose levels in type 1 diabetes: a systematic review and economic modelling (2023). NIHR Health Technology Assessment. https://doi.org/10.3310/jypl3536