Supplementary material

Title: Clinical, Economic, and Patient-Reported Benefits of Connected Insulin Pen Systems: A Systematic Literature Review

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Supplementary Table S1. Original and updated literature search strategy[a]

# ▲	Facet	Search terms	Hits (original)	Hits (update)	Total hits
1.	Disease	diabetes mellitus/ or diabetes mellitus, type 1/ or diabetes mellitus, type 2/	964,254	1,033,676	1,997,930
2.		(Type* adj ("1" or "2" or "I" or "II" or one* or two*) adj dm).ti,ab,kw.	13,674	14,946	28,620
3.		(dm2 or t2dm or t2d or t2-d or niddm).ti,ab,kw.	117,744	135,316	253,060
4.		(dm1 or t1dm or t1d or t1-d or iddm).ti,ab,kw.	60,120	66,270	126,390
5.		diabet$.ti,ab,kw.	1,666,893	1,809,519	3,476,412
6.		1 or 2 or 3 or 4 or 5	1,850,960	2,006,226	3,857,186
7.	Intervention	("smart pen*" or "smart cap*" or "smart sleeve*").mp.	142	171	313
8.		("digital pen*" or "digital cap" or "digital sleeve*").mp.	227	247	474
9.		("connected pen*" or "connected cap*" or "connected sleeve*").mp.	80	96	176
10.		("connection-enabled pen*" or "connection-enabled insulin pen*" or "connection-enabled cap*" or "connection-enabled sleeve*").mp.	0	0	0
11.		("wireless pen*" or "wireless cap" or "wireless sleeve*").mp.	18	27	45
12.		("wireless-enabled pen*" or "wireless-enabled cap*" or "wireless-enabled sleeve*").mp.	0	0	0
13.		("bluetooth pen*" or "Bluetooth-enabled pen*" or "bluetooth cap*" or "bluetoothenabled cap*" or "bluetooth sleeve*" or "bluetooth-enabled sleeve*").mp.	32	36	68
14.		(e-pen or epen or mHealth or "mobile application*" or "health application*" or "near field communication").ti,ab,kw.	19,831	26,364	46,195
15.		("connected care" or "connected system" or "cloudconnected" or "cloud connected").mp.	301	362	663
16.		("Easylog" or "Go Cap" or "GoCap" or "Insulcheck" or "Insulog" or "Tempo" or "Timesulin " or "Insulclock" or "Diabeo" or "Glooko " or "Insulia" or "Isage Rx" or "Metadixx" or "Metenda" or "My Dose Coach" or "DoseCoach" or "MyDiabby" or "MySugr " or "One Drop" or "Social Diabetes" or "Tidepool" or "Clipsulin" or "DataPen" or "ESYSTA" or "InPen" or "Novo Pen Echo Plus" or "NovoPen Echo Plus" or "NovoPen 6" or "NovoPen6" or "Pendiq2" or “Mallya”).mp.	21,084	23,813	44,897
17.		7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	41,649	51,028	92,677

# ▲	Facet	Search terms	Hits (original)	Hits (update)	Total hits
18.		6 and 17	2367	3050	5417
19.		("smart insulin*" or "digital insulin*" or "connected insulin*" or "wireless insulin*" or "wireless-enabled insulin*" or "bluetooth insulin*" or "bluetooth-enabled insulin*" or "bluetooth enabled insulin*" or "near-field communication enabled insulin*" or "nfc-enabled insulin*").mp.	128	183	311
20.		("connected diabetes care" or "digital diabetes management system" or "digital diabetes care").mp.	14	20	34
21.		((connected adj4 insulin) or (bluetooth adj4 insulin) or (digital adj4 insulin) or (smart adj4 insulin) or (wireless adj4 insulin) or ((real time or real-time) adj4 insulin) or (open-loop adj4 insulin) or (open loop adj4 insulin) or (near-field communication adj4 insulin)).mp.	1353	1502	2855
22.		18 or 19 or 20 or 21	3701	4511	8212
23.		Animals/ or In Vitro Techniques/ or experimental animal/ or animal experiment/ or animal model/ or animal cell culture/ or in vitro study/	11,614,582	12,138,239	23,752,821
24.	Applying limits	22 not 23	3355	4123	7478
25.		limit 24 to yr="2015 -Current" [Limit not valid in DARE; records were retained]	2260	568	2828
26.		limit 25 to English language [Limit not valid in CDSR,ACP Journal Club,DARE,CCA,CLCMR; records were retained]	2058	509	2567
27.	Final hits after removing duplicates	remove duplicates from 26	1385	501	1886

[a]The search strategy was the same for the original search (conducted on July 8, 2020) and updated search (conducted on May 26, 2021).

Supplementary Table S2. Inclusion and exclusion criteria for study screening

Study characteristic	Eligible	Ineligible
Population of people with diabetes	• Type 1 and type 2 PwD • All age groups	• Nonhuman
Intervention – treatment[a]	Insulin injectable treatment, specifically: Connected insulin systems: • Whole connected care eco-systems (connected injectable/pen or cap/sleeve, and app working together) • Connected insulin injection pens • Connected insulin pens that can communicate to apps/management systems • Insulin pens with the capacity to work with Bluetooth or connected cap/sleeve that can communicate to apps/management systems "Caps" or "sleeves" that enable injection pens to be "connected": • Separate Bluetooth/Near-Field Communication/connected modules that attach to an insulin pen • Diabetes management apps: • Only include apps focusing on diabetes management via injected insulin • Only include apps that are able to connect to pens/caps/sleeves	• Nonconnected insulin pens[b] • Insulin pumps[b] • Oral treatments[b] OR non-insulin injectables • On-demand treatment or those without a planned regimen[b] • Studies where people with diabetes were blinded to the data from the intervention (e.g., masked, etc.)
Intervention – comparison	• Nonconnected devices/systems/apps • Other connected devices/ systems/apps • No comparator (single-arm studies)	
Outcomes	Clinical outcomes: • HbA1c • Hypoglycemic events • MBD • Insulin Dose (average injections/ timing vs. prescribed if available) • PPBG/glycemic control • CGM captured outcomes (e.g., TIR, glucose variability, time below range, etc.) • Long-term CVD events • Diabetes complications Economic outcomes: • Direct costs • Indirect costs • Health care resource utilization PROs: • QoL • Utility • Satisfaction of the person with diabetes • Preference of the person with diabetes • Empowerment of the person with diabetes	Other outcomes not listed in the inclusion criteria

	• Self-efficacy • Distress Other Outcomes: • Outcome-based contracts • Adhere to recommendations/ glycemic monitoring/visits • Usage of, usability, or adherence to, pen/app/cap/sleeve/system and features (e.g., reminders) by the person with diabetes or HCP • HCP preference or satisfaction • Diabetes management • Attitudes to technology	
Study design	• RCTs or pragmatic trials • Single-arm trials • Non-RCT • Prospective or retrospective observational studies • Questionnaires and surveys relating to real-world clinical practice • Studies of the preference/satisfaction of the person with diabetes (DCE, utility, etc.) • Economic evaluations • Systematic literature review and meta-analysis[c]	• Case studies • Reviews • Editorials/comments • Methods papers • Animal studies
Time frame	• 2015–2021	• Publications prior to 2015 • Conference proceedings prior to 2018
Language	• English	• Non-English (except for gray literature)

[a]All connected insulin platforms (products) mentioned in Supplementary Table S1 were considered.

[b]People with diabetes could be using pumps/nonconnected pens for other insulins/oral treatments in the studies evaluated, but these were not the main intervention of interest.

[c]Systematic reviews were checked for relevant references only. Relevant white papers or reports on outcome-based contracts and local data were also searched.

CGM, continuous glucose monitoring; CVD, cardiovascular disease; DCE, discrete choice experiment; HbA1c, glycated hemoglobin; HCP, health care professional; MBD, missed bolus dose; PPBG, postprandial blood glucose; PRO, patient-reported outcome; PwD, people with diabetes; QoL, quality of life; RCT, randomized controlled trial; TIR, time in range.

Supplementary Table S3. Characteristics of included studies that contributed data for the analysis

Citation (related citation[s])	Study design[a] (country)	Study duration/ follow-up duration (weeks)	Study population	No. of people with diabetes included	Intervention/ comparator	Type of insulin/insulin pen used
RCTs						
Gomez-Peralta et al. 2020 [1]	Single-center, open-label, parallel (Spain)	4/4	T1DM	16	Insulclock®/Masked Insulclock®[b]	KwikPen (insulin lispro)
Ramos et al. 2020 [2] (Clinical trials.gov [3])	Multicenter, open-label, crossover (USA) [conference abstract]	12/12	T2DM	80	Insulclock®/Device without feedback	Basal insulin
Observational studies						
Catrina et al. 2020 [4-7][c] (Adolfsson et al. 2020 [4], 2020 [5], Jendle et al. 2020; [7] Catrina et al. 2020 [6][c])	Multicenter, prospective (Sweden)	18 months/ 167–260 days	T1DM (adults)	94	NovoPen® 6	Basal and or bolus insulin
		Up to 633 days (mean 409 days)	T1DM (children)	39		
Amante et al. 2018 [8]	Single-center, prospective (USA) [conference abstract]	4/NR	T1DM, T2DM	20	GoCap/Glucose meter	SoloSTAR (insulin glargine)
Emperra 2015 [9]	Multicenter, prospective (Germany) [white paper]	33 months/NR	T1DM, T2DM	215	ESYSTA®	Conventional insulin therapy (ICT or MDI)
Gomez-Peralta et al. 2019 [10]	Single-center, prospective (Spain) [conference abstract]	NR	T1DM	8	Insulclock®	Not specified
Polonsky et al. 2019 [11] (Eli Lilly 2018 [12], Edwards et al. 2021 [13][c])	Multicenter prospective (USA) [conference abstract]	12/NR	T1DM, T2DM	68	Bravo® pen –CGM then Bravo® pen +CGM	Insulin lispro

Smith et al. 2021 **[14]**	Prospective, real-world (USA) [conference abstract]	120 days	T1DM, T2DM	482	InPen®	Not specified
Economic studies						
Jendle et al. 2020 [15]	The IQVIA CORE Diabetes Model (Sweden)	NA	T1DM	94	NovoPen® 6	Basal and or bolus insulin
Van de Sand et al. 2019 [16]	Markov model simulations (Germany) [conference abstract]	NA	T1DM, T2DM	NR	ESYSTA®	Not specified

[a]Model design for the economic studies.

[b]People with diabetes receiving “masked” without receiving reminders and app alerts.

[c]Conference abstract.

CGM, continuous glucose monitoring; ICT, intensified conventional therapy; MDI, multiple daily injection; NA, not applicable; NR, not reported; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; USA, United States of America.

Supplementary Table S4. Summary of outcomes in the included studies

Study name	HbA1c	MBD	Insulin dose	PPBG	TIR	GV	TBR	TAR	Hypogly. events	CVD events	Adherence	ALBSS	SF-36	ITSQ	DTSQ	Other PROs[a]	Costs	Other outcomes
RCTs																		
Gomez-Peralta et al. 2020 [1][b]	✓	✓			✓	✓	✓	✓						✓				
Ramos et al. 2020 [2,3][c]	✓					✓									✓			
Observational studies																		
Catrina et al. 2020 – adults [5,7][b]		✓	✓		✓	✓	✓	✓	✓									
Catrina et al. 2020 – children [4][b]			✓		✓		✓	✓										
Amante et al. 2018 [8][d]																✓		
Emperra 2016 [9][d]	✓		✓						✓				✓					
Gomez-Peralta et al. 2019 [10][a]														✓				✓
Polonsky et al. 2019 [11,12][d]	✓	✓			✓							✓				✓		
Smith et al. 2021 [14][d]					✓		✓											

Economic studies		
Jendle et al. 2021 [15][b]	✓	✓
Van de Sand et al. 2019 [16][d]	✓	✓

[a]Other PROs included: Hypoglycemic Confidence Scale (HCS); Health Problem-Solving Skill (HPSS); Pictorial Representation of Illness and Self Measure Revised II (PRISM); General Life Stress Scale (GLSS); Big Five Inventory (BFI); and unnamed questionnaires.

[b]Indicates studies with type 1 PwD.

[c]Indicates studies with type 2 PwD.

[d]Indicates studies with both Type 1 and type 2 PwD.

ALBSS, Adult Low Blood Sugar Survey; CVD, cardiovascular disease; DTSQ, Diabetes Treatment Satisfaction Questionnaire; GV, glycemic variability; HbA1c, glycated hemoglobin; Hypogly, hypoglycemic; ITSQ, Insulin Treatment Satisfaction Questionnaire; MBD, Missed bolus dose; PPBG, postprandial blood glucose; PRO, patient-reported outcome; PwD, people with diabetes; RCT, randomized controlled trial; SF-36, Short Form 36; TAR, time above range; TBR, time below range; TIR, time in range.

Supplementary Table S5. Baseline characteristics of participants in included clinical studies and economic studies

Citation (related citation[s])	Treatment arms/ subgroups (n)	Female, %	Age, years	Type of diabetes (disease duration, years)	HbA1c, mmol/mol; %	Prior treatment	BMI, kg/m^2; weight, kg	Race %	Comorbidities, %	Currently using CGM/ FGM
Clinical trials										
Connected caps										
Gomez-Peralta et al. 2020 [1]	Overall (16)	44	40.1 ± 13.9	T1DM (20.4 ± 11.9)	NR	NR	24.8 ± 3.9; 69.4 ± 10.6	NR	Retinopathy: 37.5 Nephropathy: 12.5 Neuropathy: 31.3	Yes – CGM
	Active Insulclock® (10)	50	43.1 ± 13.8	T1DM (20.9 ± 12.5)	NR	NR	23.2 ± 3.0; 65.2 ± 9.5	NR	Retinopathy: 40 Nephropathy: 20 Neuropathy: 30	Yes – CGM
	Masked Insulclock® (no reminders) (6)	33	35.2 ± 13.8	T1DM (19.5 ± 11.9)	NR	NR	27.0 ± 4.2; 75.1 ± 10.1	NR	Retinopathy: 33.3 Neuropathy: 33.3	Yes – CGM
Ramos et al. 2020 [2,3]	Insulclock® (receiving reminders) (40)	67.5	56 ± 11	T2DM (NR)	NR; 9.2 ± 1.5	NR	NR	Black: 36 (90.0%) White: 1 (2.5%) Unknown: 3 (7.5%)	NR	NR
	Device without feedback (40)	42.5	56 ± 11	T2DM (NR)	NR; 9.2 ± 1.5	NR	NR	Black: 37 (92.5%) White: 3 (7.5%)	NR	NR
Gomez-Peralta et al. 2019 [10]	Insulclock (8)	56	Range: 21–56	T1DM (NR)	NR	NR	NR	NR	NR	NR
Amante et al. 2018 [8]	Gocap (20)	NR	NR	T1DM, T2DM (NR)	NR	NR	NR	NR	NR	Yes – glucose meter

	Glucose meter (20)	NR	NR	T1DM, T2DM (NR)	NR	NR	NR	NR	NR	Yes – glucose meter
Connected insulin pens										
Catrina et al. 2020 – adults [5]	NovoPen® 6 (94)	49	39.2 (range: 18–83)	T1DM (NR)	NR	NR	NR	NR	NR	Yes – CGM
Catrina et al. 2020 – children [4]	NovoPen® 6 (39)	NR	Children + adolescents	NR	NR	NR	NR	NR	NR	NR
Polonsky et al. 2019 [11] (Eli Lilly 2018) [12]	Connected insulin pen (68)	44.1	47.7 ± 11.6 (range: 21–65)	T1DM, T2DM (T1DM [n=40]: 22.7 ± 11.8; T2DM [n=28]: 15.9 ± 7.4)	81.4 ± 19.7; 9.6 ± 1.8	NR	30.3 ± 6.1	Hispanic/ Latino: 17.6 White: 91.2	NR	Yes – CGM
Smith et al. 2021 [14]	InPen® (482)	NR	NR	T1DM (NR) T2DM (NR)	NR	NR	NR	NR	NR	Yes – CGM
Connected insulin platform										
Emperra 2016 [9]	ESYSTA® Overall (215)	39	60	T1DM, T2DM (14.5)	NR; 8.7	ICT/MDI: 80% Other: 20%	NR	NR	NR	NR
	ESYSTA® T1DM (73)	38	45.1	T1DM (14.9)	NR	NR	NR	NR	NR	NR
	ESYSTA® T2DM (173)	39	63.3	T2DM (14.4)	NR	NR	NR	NR	NR	NR
Economic studies										
Jendle et al. 2021 [15][a]	NovoPen® 6 (NR)	45.0	41.6	T1DM (26.1)	8.27 (smart pens arm)	NR	25.3	White: 100	NR	Yes – CGM

					8.93 (standard care arm)					
Van de Sand et al. 2019 [16]	**ESYSTA® (NR)**	**NR**	**N/A**	**T1DM, T2DM (NR)**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**

Age, HbA1c, BMI, and weight are reported in mean ± SD.

[a]Jendle et al. 2021 [15] used data from Adolfsson et al. 2020 [5] for the simulation; parameters reported are for the simulated cohorts.

BMI, body mass index; CGM, continuous glucose monitoring; FGM, flash glucose monitoring; HbA1c, glycated hemoglobin; ICT, intensified conventional insulin therapy; MDI, multiple daily injections; N/A, not applicable; NR, not reported; SD, standard deviation; T1DM, type 1 diabetes; T2DM, type 2 diabetes

Supplementary Table S6. Clinical outcomes in included clinical studies[a]

Study name	Treatment arm	Sample size	Time-point	Clinical outcomes	
				Mean ± SD	Comments
Connected caps					
HbA1c					
Gomez-Peralta et al. 2020 [1]	Overall	16	Change from baseline to Week 4	–0.27%	No significant differences from baseline were observed in the change in HbA1c levels; p=0.4098
	Active Insulclock®	10		NR	–
	Masked Insulclock® (no reminders)	6			–
Ramos et al. 2020 [2,3]	Insulclock®	80 (40 per group)	Baseline	9.2 ± 1.5%	–
	Device without feedback				–
	Insulclock®		Change from baseline to Week 12	–0.9%	HbA1c improved significantly from baseline
	Device without feedback			–0.7%	
MBD					
Gomez-Peralta et al. 2020 [1]	Overall	16	Change from baseline to Week 4	Number of mistimed insulin doses: –5.4 (p=0.032) Number of missed insulin doses: –3.9 (p=0.135)	A decrease in numbers per month is reported
	Active Insulclock®	10		NR	–
	Masked Insulclock® (blinded group)	6		NR	–
TIR					
Gomez-Peralta et al. 2020 [1]	Overall	16	Change from baseline to Week 2	+7%	Increased TIR after 2 weeks p=0.038 vs. baseline

	Active Insulclock®	10		+8%	p=0.026 vs. baseline
	Masked Insulclock® (blinded group)	6		NR	–
Glycemic variability					
Gomez-Peralta et al. 2020 [1]	Overall	16	Change from baseline to Week 2	SD:-14.4mg/dl (0.8 mmol/L)	Glycemic control and variability. p=0.003 vs. baseline
	Active Insulclock®	10		NR	–
	Masked Insulclock® (blinded group)	6		SD: –18.5 mg/dL (1.0 mmol/L)	p=0.037 vs. baseline
TBR					
Gomez-Peralta et al. 2020 [1]	Overall	16	Change from baseline to Week 2	+5.3%	p=0.0826 vs. baseline
	Active Insulclock®	10		NR	–
	Masked Insulclock® (blinded group)	6		NR	–
TAR					
Gomez-Peralta et al. 2020 [1]	Overall	16	Change from baseline to Week 2	–12.5%	p=0.0026 vs. baseline
	Active Insulclock®	10		NR	–
	Masked Insulclock® (blinded group)	6		NR	–
Hypoglycemic events, n (%)					
Ramos et al. 2020 [2,3]	Insulclock®	40	Week 24	Hypoglycemia: 29 (72.5%) Severe Hypoglycemia: 1 (2.5%)	–
	Device without feedback	40		Hypoglycemia: 25 (62.5%) Severe Hypoglycemia: 1 (2.5%)	–
CVD-related adverse events, n (%)					

Ramos et al. 2020 [2,3]	Insulclock®	40	Week 24	SAE: Heart failure readmission: 0 Stroke: 1 (2.5%) Other (non-SAE) AEs CHF shortness of breath: 0 Hypertension: 0	–
	Device without feedback	40		SAE: Heart failure readmission: 1 (2.5%) Stroke: 0 Other (Non-SAE) AEs CHF shortness of breath: 1 (2.5%) Hypertension: 1 (2.5%)	Number of events for heart failure readmission: 2
Other adverse events, n (%)					
Ramos et al. 2020 [2,3]	Insulclock®	40	Week 24	SAE: Wound Infection: 0 Surgical Procedures: 0 Other (Non-SAE) AEs Ear infection: 0 Hyperglycemia: 1 (2.5%) Hypoglycemia: 2 (5.0%) Nausea and vomiting: 1 (2.5%) Epigastric pain: 1 (2.5%) Pain: 0 Leg swelling: 0 Abdominal pain: 0	–

		Nonserious work-related muscular injury: 0 Back pain: 1 (2.5%) Toe injury: 1 (2.5%) Chest pain of muscular etiology: 1 (2.5%) Diabetic neuropathy: 0 Asthma: 0	
Device without feedback	40	SAE Wound Infection: 1 (2.5%) Surgical Procedures: 2 (5.0%) Other (Non-SAE) AEs Ear infection: 1 (2.5%) Hyperglycemia: 0 Hypoglycemia: 0 Nausea and vomiting: 0 Epigastric pain: 0 Pain: 1 (2.5%) Leg swelling: 1 (2.5%) Abdominal pain: 2 (5.0%) Nonserious work-related muscular injury: 1 (2.5%) Back pain: 0 Toe injury: 1 (2.5%) Chest pain of muscular etiology: 2 (5.0%) Diabetic neuropathy: 1 (2.5%) Asthma: 1 (2.5%)	–
Connected insulin pens			
HbA1c			

Polonsky et al. 2019 [11]	Bravo® pen	68	Baseline	9.6 ± 1.8%; 81.4 ± 19.7 mmol/mol	–
			1st 6 weeks	8.7 ± 1.4%; 72 ± 15 mmol/mol	"Blinded period"
			2nd 6 weeks	8.3 ± 1.4%; 67 ± 15 mmol/mol	"rtCGM" period
			Change at 12 weeks (rtCGM vs. blinded)	–0.43 (CI: –0.63 to –0.24); –4.7 (95% CI: –6.9 to –2.6) mmol/mol	p<0.001, rtCGM vs. blinded
MBD					
Catrina et al. 2020 – adults [5]	NovoPen® 6	81	Baseline	0.74 (95% CI: 0.62 to 0.88)	Mean daily number of MBD meals is reported MBD was defined as meals with no bolus injection within –15 to +60 mins from the start of the meal, as detected by algorithm
			6 months	0.42 (95% CI: 0.30 to 0.60); p=0.002	A significant decrease of 43% in the average daily number of MBD meals was observed from baseline to after ≥5 HCP visits Based on the assumption that people with diabetes have three main meals per day, this corresponded to a decrease from 24.7% (95% CI: 20.8 to 29.4) to 14.1% (95% CI: 9.9 to 19.9) in MBD injections
Catrina et al. 2020 – adults [7]	NovoPen® 6	96	Baseline	0.32 (95% CI: 0.26 to 0.39)	Mean number of late-bolus doses/day is reported
			Follow-up	0.18 (95% CI: 0.13 to 0.27)	–
			Change from baseline to after ≥5 HCP visits	42% reduction	p=0.005 vs. baseline
	Bravo® pen	65	Baseline	0.94 ± 0.39/day	–

Polonsky et al. 2019 [11]			21 days	0.72 /day (range 0–1.86)	MBD daily frequency was significantly associated with TIR (Spearman's correlation coefficient [r]= –0.28, p=0.02) and TAR (r=0.26, p=0.03) Baseline predictors of MBD included HbA1c (incidence rate ratio, IRR = 1.118, p=0.003) and BMI (IRR=0.969, p=0.008)
			1st 6 weeks (Blinded period)	0.95 ± 0.42/day: 25.5 ± 12.7%/month	Missed bolus opportunities
			2nd 6 weeks (rtCGM)	0.94 ± 0.44/day 24.9 ± 10.9 %/month	Missed bolus opportunities
			Change at 12 weeks (rtCGM vs. blinded)	0.004/day (CI: –0.086 to 0.077); –0.61%/ month (CI: –2.9 to 1.72)	p=0.92, rtCGM vs. blinded (per day) p=0.60, rtCGM vs. blinded (per month)
Insulin dose					
Catrina et al. 2020 – adults [5]	NovoPen® 6	81	Baseline	NR	A significant increase in bolus insulin dose (n=81) from baseline to after ≥5 HCP visits of 27.9%/day was observed There was no significant change in mean basal insulin dose (n=22)
			6 months	32.1 U/day	–
			Change at 6 months	28% increase	A significant increase in injected bolus dose from baseline to follow-up period (28%)
TIR					
Catrina et al. 2020 – adults [5]	NovoPen® 6	81	Baseline	9.2 hours/day	TIR (3.9–10.0 mmol/L)
			6 months	11.1 hours/day	TIR (3.9−10.0 mmol/L) after ≥5 HCP visits (median time in study: 6 months)
			Change from baseline	1.9 hours/day; p=0.0009	–

Catrina et al. 2020 – children [4]	NovoPen® 6	39	12 months	NR	TIR was not significantly affected (value not given)
Polonsky et al. 2019 [11]	Bravo® pen	68	Baseline	NR	–
		68	21 days	42.6 ± 18.8	–
		65	1st 6 weeks (Blinded period)	42.5 ± 19.2	Data From CGM and the connected insulin pen were used to identify and quantitate MBD, defined as an 80 mg/dL (4.4 mmol/L) glucose increase in ≤2 hours not preceded within 1 hour by an insulin dose TIR: glucose levels between 70–180 mg/dL (3.9−10 mmol/L)
			2nd 6 weeks (rtCGM)	49.6 ± 20	–
			Change at 12 weeks	7.13 (CI: 3.7 to 10.5)	Change at 12 weeks (rtCGM vs. blinded) p<0.001
Smith et al. 2021 [14]	InPen®	636	60 days pre-initiation	60.27%	
			60 days post-initiation	60.03%	
			Change at 120 days	0.24%	No significant decrease in TIR was reported
Glycemic variability					
Catrina et al. 2020 – adults [5,7]	NovoPen® 6	96	Baseline	NR	A significant correlation between the timing of bolus dose and coefficient of variation (CV) of CGM signal was found; each 10-min delay of bolus dose was associated with an increase of 0.5% CV (p<0.0001) on average
TBR					
Catrina et al. 2020 – adults [5]	NovoPen® 6	81	Baseline	L1: 0.69 hours (95% CI: 0.55 to 0.83)	Time in hypoglycemia L1 (3.0-3.9 mmol/L) Time in hypoglycemia L2 (<3.0 mmol/L)

				L2: 0.47 hours (95% CI: 0.32 to 0.61)	
			6 months	NR	–
			Change from baseline	L1: 0.15 hours (95% CI: –0.36 to 0.07); p=0.181 L2: 0.33 hours (95% CI: –0.56 to -0.10); p=0.05	There was no change in time in L1 hypoglycemia (3.0−3.9 mmol/L; p=0.181)
Catrina et al. 2020 – children [4]	NovoPen® 6	39	12 months	NR	Time-in-hypoglycemia decreased after 12 months (p=0.03 vs. baseline)
Smith et al. 2021 [14]	InPen®	636	60 days pre-initiation	2.54%	
			60 days post-initiation	2.27%	
			Change at 120 days	–0.27% (95% CI: –0.41, –0.12%)	p=0.0002 pre- vs. post-smart pen initiation
TAR					
Catrina et al. 2020 – adults [5]	NovoPen® 6	81	Baseline	11.80 hours (95% CI: 10.81 to 12.79)	Time-in-hyperglycemia (>10 mmol/L)
			6 months	NR	–
			Change at 6 months	–1.78 hours (95% CI: –2.96 to –0.60)	Significant reduction in TAR (>10 mmol/L) (p=0.003) was observed
Catrina et al. 2020 – children [4]	NovoPen® 6	39	12 months	NR	Time-in-hyperglycemia was not significantly affected (value not given)
Polonsky et al. 2019 [11]	Bravo® pen	68	Baseline	NR	
			21 days	52.8 ± 21.3	
			1st 6 weeks (Blinded period)	NR	

			2nd 6 weeks (rtCGM)	NR	
Hypoglycemic events					
Catrina et al. 2020 – children [4]	NovoPen® 6	39	Baseline	NR	
			6 months	12% (95% CI: –27 to 7)	Percentage decrease from baseline (incidence of hypoglycemia) p=0.19 vs. baseline
			12 months	31% (95% CI: –44 to –16)	Percentage decrease from baseline (incidence of hypoglycemia) p<0.001 vs. baseline
Connected insulin platform					
HbA1c					
Emperra 2016 [9]	ESYSTA®	215	Baseline	8.7%	–
			3 (±1) months	8.0%	P-value <0.001 vs. baseline
			6 (±1) months	8.0%	P-value <0.001 vs. baseline
			9 (±1) months	7.9%	P-value <0.001 vs. baseline
			12 (±1) months	7.9%	P-value <0.001 vs. baseline
			15 (±1) months	7.8%	On average overall reduction in HbA1c was 0.9% points. For type 2 PwD, reduction was by 2% points
Hypoglycemic events					
Emperra 2016 [9]	ESYSTA®	215	Baseline	NR	Despite a reduction in HbA1c value and therefore a significantly lower BG profile, no increase in the number of hypoglycemic episodes was observed The comparison data available from the health insurance company showed no
			3 months	NR	
			6 months	NR	
			9 months	NR	

	12 months	NR	(emergency) hospital admissions due to hypoglycemia in the ESYSTA intervention group during the study period
	15 months	NR	

[a]Values are in mean ± SD unless specified.

AE, adverse event; BG, blood glucose; CGM, continuous glucose monitor; CHF, congestive heart failure; CI, confidence interval; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; HCP, health care professional; MBD, missed bolus dose; NR, not reported; rtCGM, real-time continuous glucose monitor; SD, standard deviation; PwD, people with diabetes; SAE, serious adverse event; TAR, time above range; TBR, time below range; TIR, time in range.

Supplementary Table S7. Patient-reported outcomes in included clinical studies

Study name	Treatment arm	N	Name of scale	Time-point	Outcomes		
					n (%)	Mean ± SD score	Comments
Connected caps							
Gomez-Peralta et al. 2020 [1]	Insulclock®	16	ITSQ	At 4 weeks	NR	NR	Most of the items of the ITSQ improved after 4 weeks of Insulclock use. Significant differences were observed in "perception of insulin treatment interference in work/school activities" (all groups) and for "potential of current insulin treatment for avoiding severe hypoglycemic episodes" items (masked group) [p<0.05]
Ramos et al. 2020 [2,3]	Insulclock®	40	DTSQc survey	Change at 12 weeks	NR	15.5 ± 3.7	People with diabetes were equally satisfied with the device during intervention and control
	Device without feedback	40	DTSQc survey	Change at 12 weeks	NR	15.2 ± 3.1	NR
	Insulclock®	40	Treatment adherence	Week 0 through Week 24	NR	22.22 ± 25.12	Treatment adherence refers to a number of insulin injection irregularities and it measures "omission, mistiming, and dosing"
	Device without feedback	40	Treatment adherence	Week 0 through Week 24	NR	23.10 ± 26.75	
Gomez-Peralta et al. 2019 [10]	Insulclock®	8	ITSQ	Change from baseline	NR	Total: –0.11	The ITSQ showed a self-perceived benefit with Insulclock® use

Amante et al. 2018 [8]	GoCap®	20	Questionnaire	≥1 month	Perceptions of ease of use: 16 (80)	NR	After ≥1 month, focus groups and semi-structured phone interviews were conducted
					Usefulness of the devices: 15 (75)	NR	
Connected insulin pens							
Polonsky et al. 2019 [11,12]	Connected insulin pen	68	HCS	Baseline	NR	3.2 (range: 1.8–4.0)	
				1st 6 weeks (Blinded CGM)	NR	No change	
				2nd 6 weeks (rtCGM)	NR	No change	
			ALBSS	Baseline	NR	13.7 (range: 0.0–34.0)	
				1st 6 weeks (Blinded CGM)	NR	13.3 (range: 0.0–32.0)	
				2nd 6 weeks (rtCGM)	NR	12.9 (range: 0.0–38.0)	
			HPSS	Baseline	NR	14.6	
				1st 6 weeks (Blinded CGM)	NR	14.8	Mean increase: 0.21
				2nd 6 weeks (rtCGM)	NR	14.8	Mean increase: 0.24
			PRISM	Baseline	Subjects with small IPM (7.4)	NR	
				1st 6 weeks (Blinded CGM)	Subjects with small IPM (13.2)	NR	

				2nd 6 weeks (rtCGM)	Subjects with small IPM (32.4)	NR	
			GLSS	Baseline	NR	Mean total scores: 7.7	
				1st 6 weeks (Blinded CGM)	NR	Mean total scores: 8.1	
				2nd 6 weeks (rtCGM)	NR	Mean total scores: 8.1	
		78	BFI	Blinded CGM study period	NR	3.89 ± 0.67	BFI Conscientiousness score (range 1 to 5)
Connected insulin platform							
Emperra 2016 [9]	ESYSTA®	215	SF-36	Change from baseline	NR	NR	The greatest changes are seen on the “physical pain” scales (+12.5% points) and “emotional role function” (+8.8%)
			Questionnaire	NR	ESYSTA recommendation to others by: People with diabetes (84) Doctors (93)	NR	More than 75% of the participants continued to use the system beyond the end of the project

ALBSS, Adult Low Blood Sugar Survey (potential score range 0–44, higher score represents greater fear); BFI, Big Five Inventory (1–5 point Likert scale over five personality factors); CGM, continuous glucose monitoring; DTSQc, Diabetes Treatment Satisfaction Questionnaire change (potential score range –18 to 18, higher score indicates greater improvement in satisfaction; GLSS, General Life Stress Scale (potential score range 0–24, higher score indicates greater overall life stress); HCS, Hypoglycemic Confidence Scale (potential range 1–4.0, higher score indicates higher confidence); HPSS, Hypoglycaemia Problem-Solving Scale; IPM, Illness perception measure; ITSQ, Insulin Treatment Satisfaction Questionnaire (potential score range 0–100%, higher score indicates better treatment satisfaction); NR, not reported; PRISM, Problem Recognition in Illness Self-Management survey; rtCGM, real-time CGM; SD, standard deviation; SF-36, Short Form 36.

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