Supplementary Material

Closed-Loop Insulin Delivery versus Sensor-Augmented Pump Therapy in Older Adults with Type 1 Diabetes (ORACL): A Randomized, Crossover Trial

Contents:

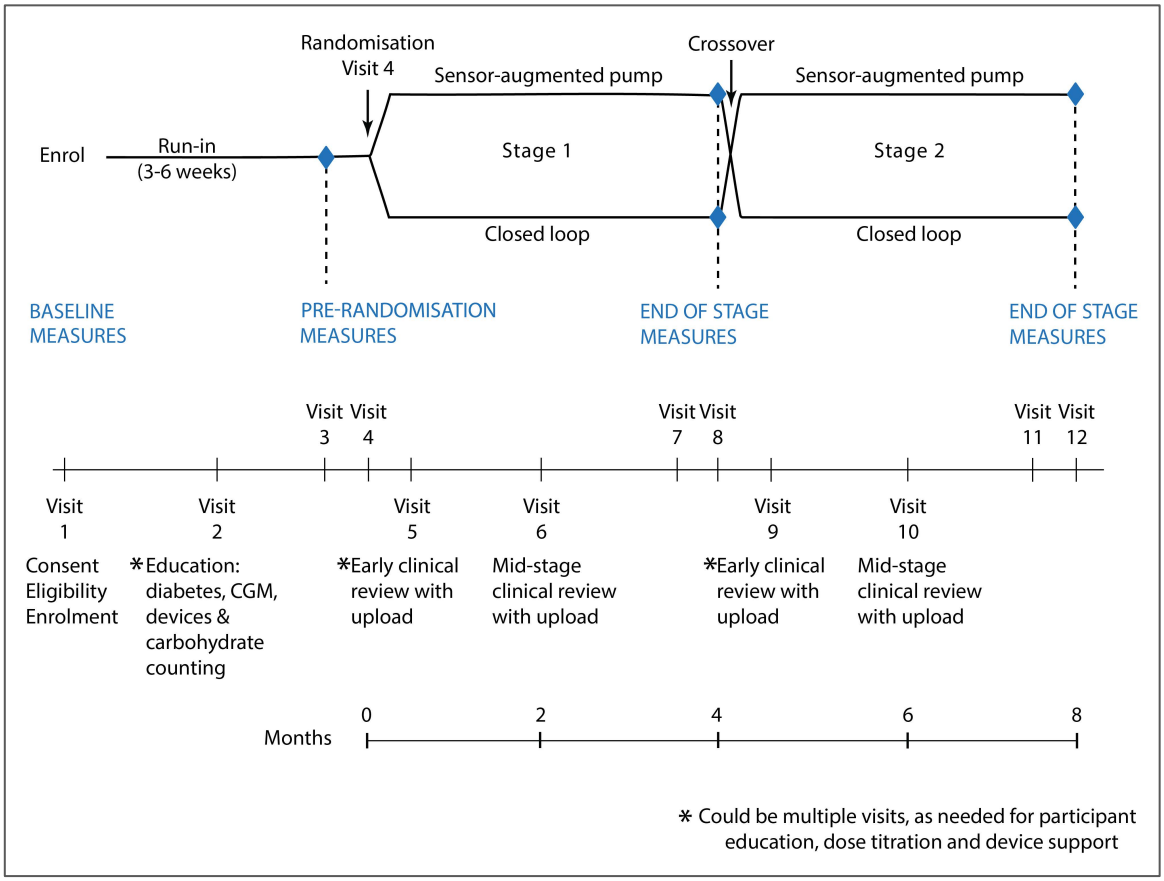

Figure S1: Trial design

Table S1: Eligibility criteria

Inclusion criteria

- Age ≥60 years
- Type 1 diabetes (consistent with ADA classification) for ≥10 years, as judged by the Investigator
- Using insulin pump therapy (≥1-year pump experience), with established insulin delivery settings
- Treated with a rapid-acting insulin analogue
- HbA_{1c} ≤10.5% (≤91 mmol/mol)
- Able to use the study devices (with or without caregiver assistance, though able to troubleshoot independently during device use)
- English language proficiency
- Internet and cellular phone coverage at home
- Understands study protocol; willing and able to meet all protocol requirements

Exclusion criteria

- Non-type 1 diabetes (including diabetes secondary to chronic disease)
- Use of closed-loop insulin delivery within the past 3 months
- Nephropathy with eGFR <30 mL/min/1.73m^2, measured within past 3 months, or on dialysis
- Use of any glucose-lowering agent other than insulin within the past 3 months
- Corticosteroid medication within the past 3 months (or anticipated during the study period)
- Inability to tolerate adhesives in the area of sensor placement (e.g. due to skin disease, intolerance to adhesives)
- Untreated coeliac disease or other malabsorption
- Uncontrolled thyroid disease
- Clinically significant gastroparesis
- Haemoglobinopathy, sickle cell disease, or has received red blood cell transfusion or erythropoietin within past 3 months
- Uncontrolled hypertension (blood pressure: diastolic >100 mmHg or systolic >160 mmHg)
- History of myocardial infarction, severe uncontrolled heart failure, unstable angina, transient ischemic attack, stroke, or thromboembolic disease in the past 3 months
- Visual or hearing impairment precluding use of the study devices
- Clinical diagnosis of moderate or severe dementia
- Any severe or unstable physical or psychological condition which, as judged by the Investigator, could compromise the ability to meet protocol requirements or interpretation of study results

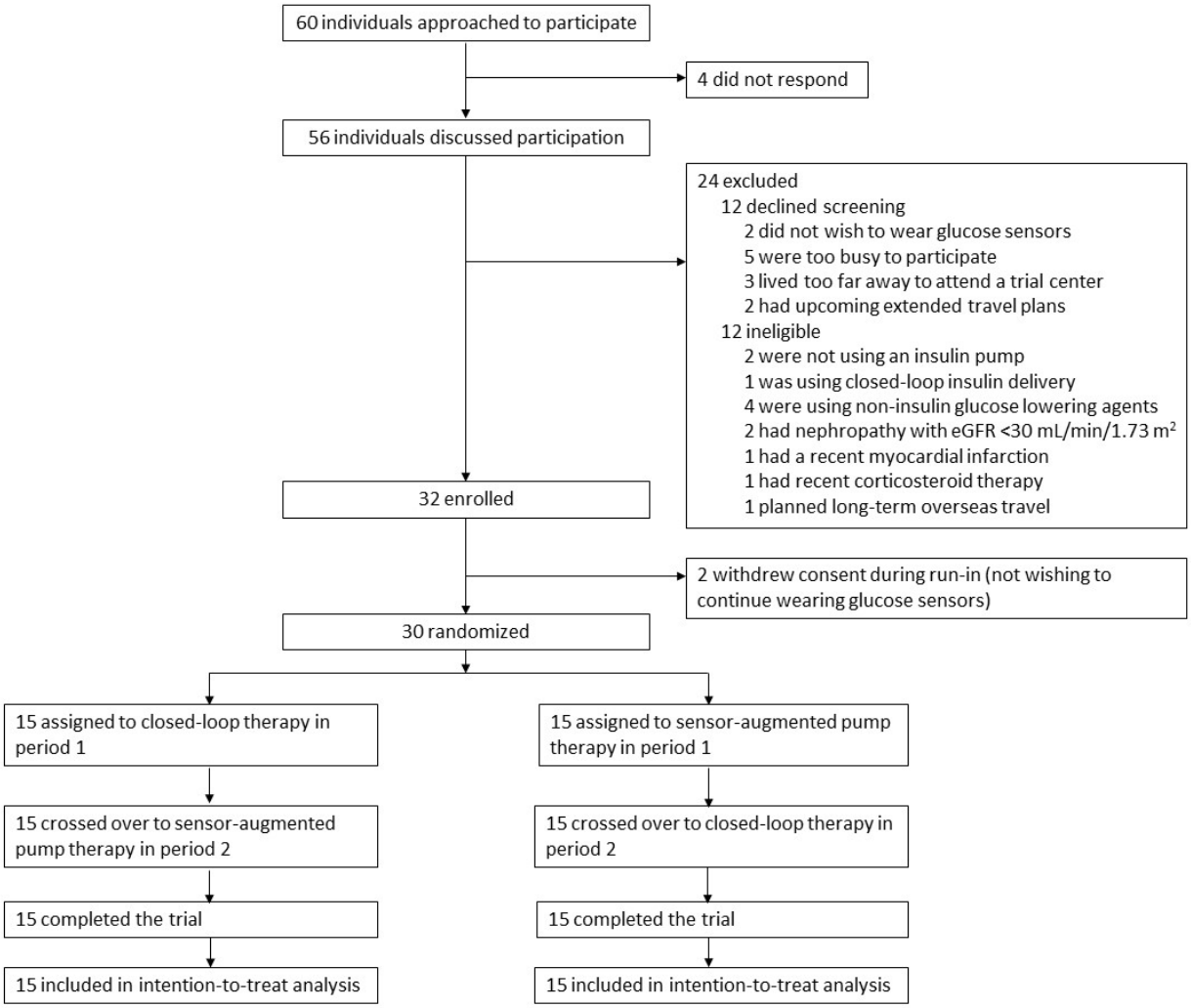

Figure S2: Trial profile

Table S2: Other clinical and cognitive functioning secondary outcomes

	Closed-loop stage (n=30)	Sensor-augmented pump stage (n=30)	Difference	*P* value
Clinical outcomes				
Functional ability				
Katz ADLs	6 (6–6)	6 (6–6)	0 (0 to 0)	>0.99
Lawton-Brody Instrumental ADLs	8 (8–8)	8 (8–8)	0 (0 to 0)	>0.99
Frailty				
FRAIL scale	0 (0–0)	0 (0–0)	0 (0 to 0)	0.60
Mini Nutritional Assessment	14 (13–14)	13.5 (12–14)	0 (0 to 1)	0.18
Sarcopenia SARC-F	1 (0–1)	0 (0–1)	0 (0 to 1)	0.34
Walking speed (m/sec)	1.24 (0.23)	1.31 (0.29)	-0.06 (-0.16 to 0.03)	0.19
Grip strength*	31.6 (8.0)	32.9 (9.5)	-0.9 (-3.1 to 1.2)	0.39
Physical Activity	4 (3–4)	4 (3–4)	0 (0 to 0)	0.86
Diabetes-related ambulance attendances	1	0	n/a	n/a
Diabetes-related hospitalizations	1	2	0.5 (0.1 to 5.5)	0.57
Incident falls	8	2	3.5 (0.7 to 16.9)	0.12
Incident delirium	0	0	n/a	n/a
Incident pressure sores	0	1	n/a	n/a
Incident infections	6	11	0.5 (0.2 to 1.7)	0.26
Cognitive functioning outcomes				
Montreal Cognitive Assessment (MoCA)	27 (27–28)	27 (26–29)	-1 (-1 to 1)	0.68
Mini-Mental State Assessment (MMSE)	30 (30–30)	30 (29–30)	0 (0 to 0)	0.58
Verbal IQ – National Adult Reading Test	40.5 (33–44)	39 (35–42)	0 (-2 to 2)	>0.99
Executive functioning: Trails Making Task B	62 (55–90)	76 (62–88)	-12 (-20 to 2)	0.072
Psychomotor speed				
Symbol Digit Modalities Test (no. correct)	44 (40–49)	44.5 (39–48)	0 (-2 to 1)	>0.99
Trails Making Task A, sec	25.3 (23.0–31.8)	24.7 (21.8–31.0)	1.4 (-1.0 to 3.0)	0.084
Grooved pegboard (dominant), sec	87 (80–95)	81 (75–90)	5 (-1 to 14)	0.057
Grooved pegboard (non-dominant), sec	91.5 (87–101)	93 (83–100)	-1 (-10 to 6)	>0.99

Results presented as mean (SD) or median (interquartile range), analyses using period-adjusted mixed effect linear regression or period-adjusted sign test, respectively. Differences presented as mean or median difference (95% CI). Due to low incidence of ambulance attendances, hospitalizations, falls, delirium, pressure sores and infections, odds of having at least one event are presented (with 95% confidence intervals), analysis by conditional logistic regression. *Includes adjustment for sex.

Table S3: Safety outcomes

	Closed-loop stage (n=30)	Sensor-augmented pump stage (n=30)
Severe hypoglycemia events *		
Number of events	3 †	2 ‡
Number of participants	3 (10%)	2 (7%)
Serious adverse events		
Number of events	0	2
Number of participants	0 (0%)	2 (7%)
Number of events by type:		
Diabetic ketoacidosis §	0	1
Other serious adverse event not related to study device #	0	1

Adverse events are reported for all participants in the trial (n=30). Data are n or n (%).

* Severe hypoglycemia was defined as a hypoglycemic event requiring the assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions to resolve.

† The three severe hypoglycemia events during the closed-loop stage each occurred after low-glucose alerts and involved another person being required to prompt the participant to ingest oral carbohydrate. No hypoglycemia-related seizures or loss of consciousness occurred. In one event only, third-party assistance was required due to altered consciousness; this event occurred during a closed-loop exit period (with no valid sensor readings and manual insulin dose determination for >4 h prior). The other two events occurred during automated basal insulin delivery (one during gardening and the other after an extra insulin bolus dose was given without carbohydrate); neither of these involved altered consciousness.

‡ The two severe hypoglycemia events during the sensor-augmented pump stage occurred when the basal insulin delivery was suspended and after low-glucose alerts; both events involved another person being required to prompt the participant to ingest oral carbohydrate. No hypoglycemia-related seizures or loss of consciousness occurred. In one event only, third-party assistance was required due to altered consciousness. In the other event, a prandial insulin bolus dose had been delivered and then the meal was delayed; there was no altered consciousness.

§ The diabetic ketoacidosis event was attributed to insulin delivery line blockage.

One participant was admitted to hospital for surgical treatment of an acute vitreous hemorrhage.

Table S4: Glucose metrics by trial sequence

Trial stage	Stage 1		Stage 2	
Allocation	**Closed loop (n=15)**	**Sensor-augmented pump (n=15)**	**Closed loop (n=15)**	**Sensor-augmented pump (n=15)**
Proportion of time at glucose concentration				
3.9–10.0 mmol/L	75.9% (69.0, 79.9)	66.6% (59.5, 72.9)	77.5% (71.3, 81.7)	70.9% (67.4, 78.3)
3.9–7.8 mmol/L	47.2% (44.3, 51.2)	40.2% (33.1, 48.7)	48.6% (44.3, 57.2)	44.5% (39.3, 50.8)
>10.0 mmol/L	23.4% (18.8, 30.0)	31.2% (20.9, 39.9)	22.0% (16.1, 28.0)	27.8% (18.1, 31.8)
>13.9 mmol/L	4.1% (2.1, 7.0)	7.2% (3.2, 12.0)	3.2% (2.2, 5.5)	4.6% (2.1, 7.9)
>16.7 mmol/L	0.74% (0.49, 1.52)	1.81% (0.81, 4.30)	0.53% (0.31, 1.32)	0.84% (0.42, 2.37)
<3.9 mmol/L	0.86% (0.60, 1.63)	1.72% (0.91, 2.67)	1.57% (0.51, 1.84)	1.66% (1.08, 2.14)
<3.3 mmol/L	0.25% (0.10, 0.40)	0.59% (0.19, 0.81)	0.41% (0.14, 0.63)	0.38% (0.20, 0.73)
<3.0 mmol/L	0.12% (0.02, 0.17)	0.26% (0.07, 0.44)	0.19% (0.04, 0.33)	0.15% (0.10, 0.36)
Mean glucose concentration, mmol/L	8.5 (8.2, 8.8)	8.8 (7.9, 9.6)	8.4 (7.8, 8.8)	8.5 (7.9, 9.0)
SD of glucose concentration, mmol/L	2.6 (2.3, 2.9)	3.2 (2.8, 3.5)	2.5 (2.4, 2.9)	2.8 (2.6, 3.1)
Coefficient of variation of glucose concentration	31.4% (29.2, 34.2)	35.4% (33.9, 36.3)	31.2% (29.9, 33.9)	34.5% (31.3, 36.0)
HbA_{1c}, %	7.4 (7.2, 7.5)	7.5 (7.1, 7.9)	7.3 (6.9, 7.5)	7.5 (7.2, 7.8)
HbA_{1c}, mmol/mol	57 (55, 59)	59 (54, 63)	56 (52, 58)	58 (55, 62)

Results are presented as median (IQR). Glucose outcomes are for the final 3 months of each stage.

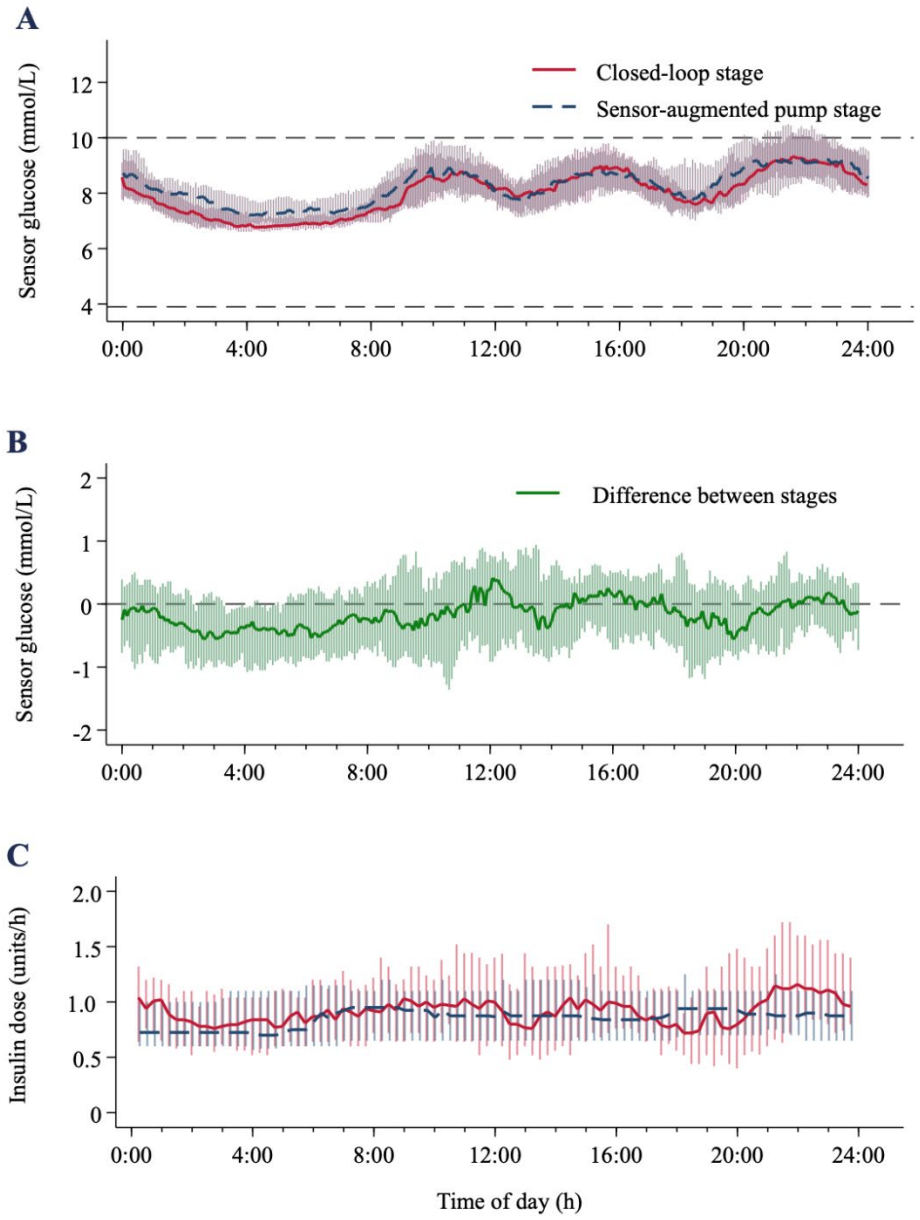

Figure S3: Sensor glucose concentration and insulin delivery profiles

(A) Within participant median sensor glucose concentration during closed-loop and sensor-augmented pump trial stages from midnight to midnight (lines indicate median, shaded areas indicate IQR). (B) Sensor glucose concentration individual paired differences between stages (lines indicate median, shaded areas indicate IQR). (C) Insulin dose delivery during closed-loop and sensor-augmented pump stages from midnight to midnight (lines indicate median, shaded areas indicate IQR).

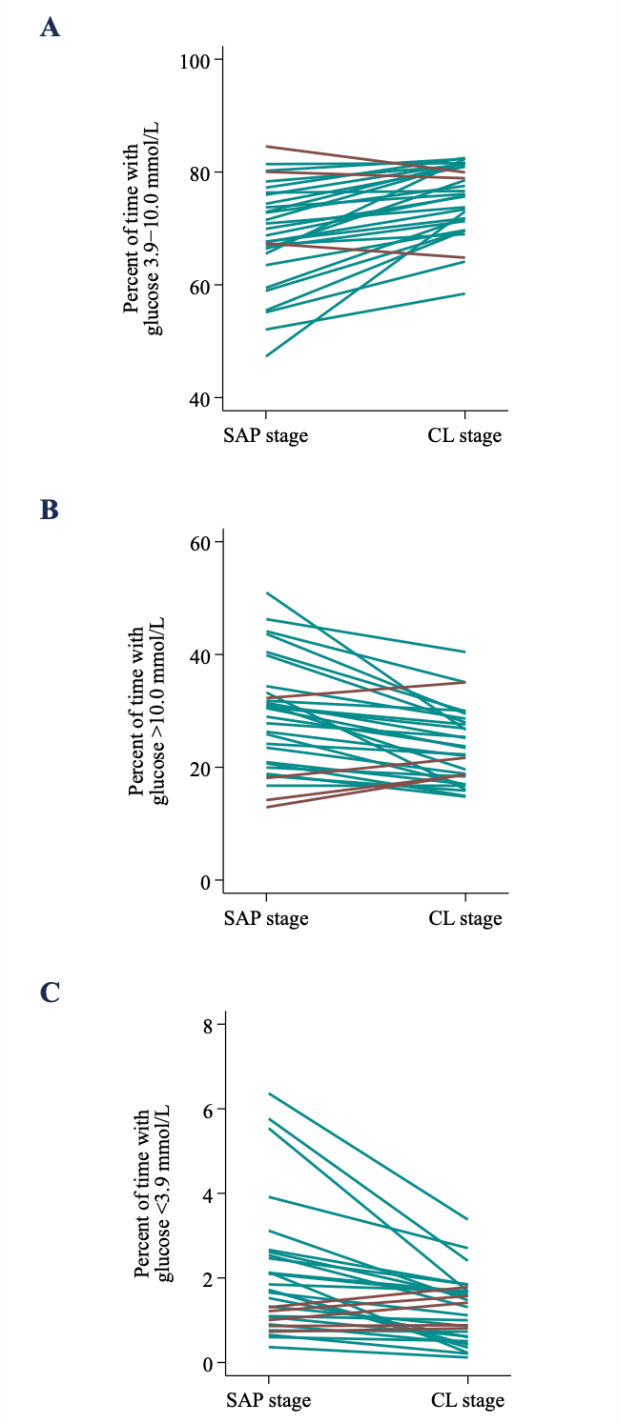

Figure S4: Individual results for continuous glucose monitoring metrics

Results are presented independent of trial sequence. Each panel represents the proportion of time spent with sensor glucose concentration within specified threshold: (A) Glucose in range 3.9–10.0 mmol/L; (B) Glucose above 10.0 mmol/L; (C) Glucose below 3.9 mmol/L. Teal lines – higher time in range, lower time above/below range, in the CL stage. Brown lines – higher time in range, lower time above/below range, in the SAP stage. SAP=sensor-augmented pump. CL=closed loop.

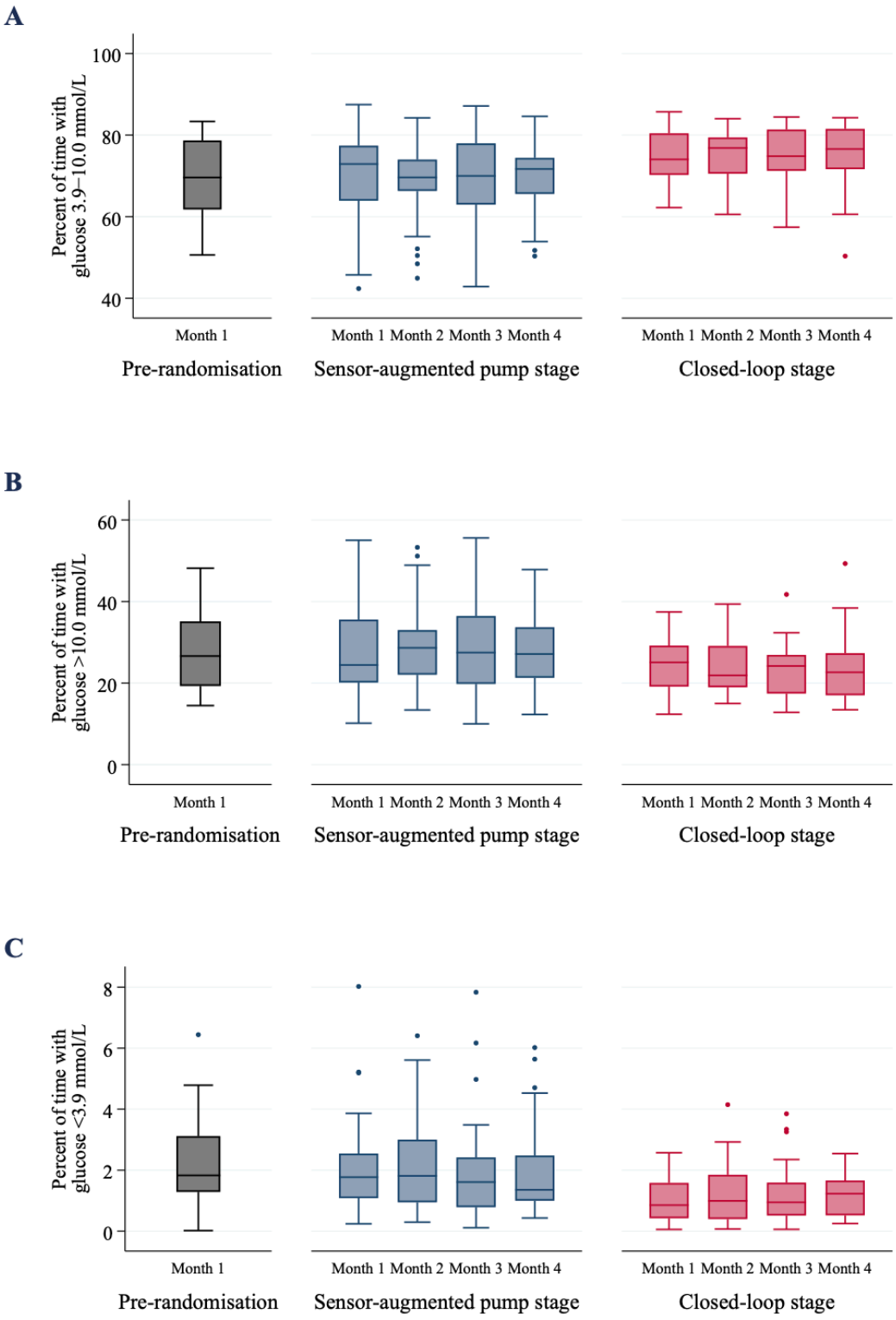

Figure S5: Continuous glucose monitoring metrics by trial month.

Boxplots representing monthly time blocks, by trial stage: black, pre-randomization; blue, sensor-augmented pump stage; red, closed-loop stage. The boxes represent interquartile range (IQR), with horizontal line at median; the whiskers represent 1.5 times the IQR; and dots represent outlier points. Results are presented independent of trial sequence.

Appendix – ORACL Trial Investigators

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