UNIVERSITY OF CAMBRIDGE

Closed-loop in populations beyond type 1 diabetes

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Disclosures

CB reports Consultancy fees from CamDiab and Speaker honoraria from Ypsomed

Content

- Fully closed-loop in the **inpatient setting**
- Closed-loop for people with **type 2 diabetes**
- Closed-loop for people with **cystic fibrosis related diabetes**

Closed-loop to manage INPATIENT diabetes

- **Prevalence of diabetes in the hospital is increasing:** ~20% of hospital beds are occupied by someone with diabetes (National Diabetes Inpatient Audit 2019).

- Maintaining near normoglycaemia during hospital admissions with current insulin therapy (multiple daily subcut insulin injections) titrated according to capillary blood glucose measurements can be **very challenging**.

- Attempts to achieve target glucose levels:
  - can **increase the risk of hypoglycaemia**
  - **increases workload** for healthcare professionals

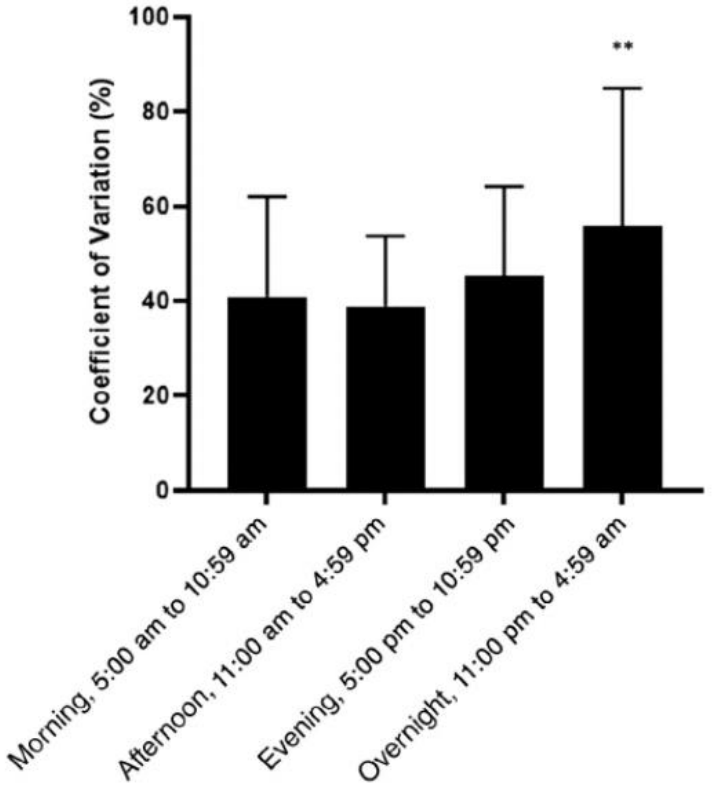
Day-to-day variability of insulin requirements in the inpatient setting is high

Inpatients with diabetes have:

- higher rates of infection
- longer length of stay
- higher readmission rates
- higher risk of mortality

Challenges:

- Metabolic response to acute illness
- Inconsistent oral intake and periods of fasting
- Use of corticosteroids
- Use of enteral/parenteral nutrition
- Workload burden
- Fear of hypoglycaemia
- Lack of evidence based guidelines



Day to day variability of insulin requirements in the inpatient setting is high

Boughton et al Diabetes Obes Metab. 2021

Background

- Current inpatient diabetes therapy is sub-optimal and often results in patient harm.
  - Both hyper- and hypoglycaemia in hospital are associated with **increased risk of complications, length of stay, admission to ICU and mortality**.
  - This has significant cost implications for hospitals.

- RCT data shows that glucose sensors alone **do not significantly improve glycaemic control** or reduce time in hypoglycaemia compared to finger-stick glucose

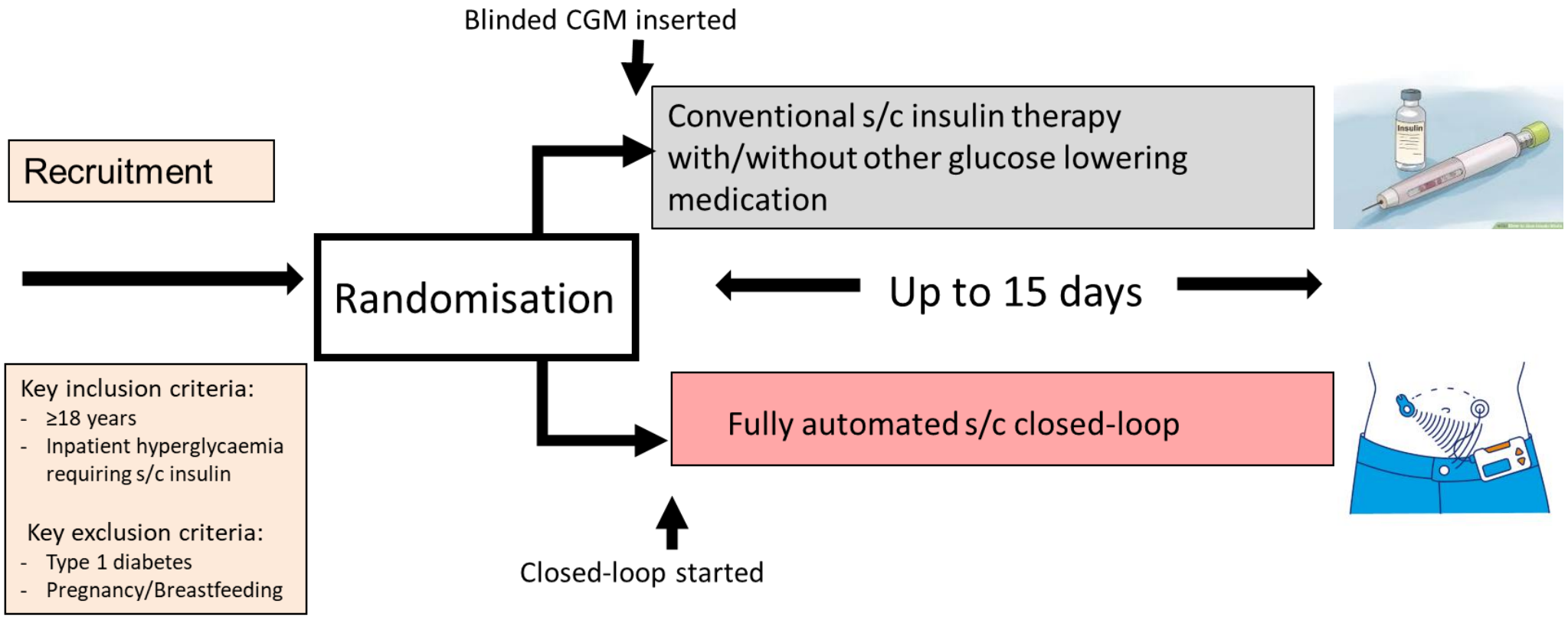
	Overall (*N* = 162)	POC-guided (*N* = 79)	CGM-guided (*N* = 83)	*P* value
Glycemic control				
TIR % 70–180 mg/dL	51.65 ± 26.2	48.64 ± 24.2	54.51 ± 27.7	0.14
TBR % <70 mg/dL	1.40 ± 4.45	2.15 ± 5.91	0.69 ± 2.15	0.43
TBR % <54 mg/dL	0.65 ± 2.79	1.00 ± 3.74	0.32 ± 1.33	0.35
TAR % >180 mg/dL	46.95 ± 26.76	49.21 ± 25.50	44.80 ± 27.89	0.26

Spanakis et al. Diabetes Care 2022

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Closed-Loop Insulin Delivery for Glycemic Control in Noncritical Care



Primary endpoint: Proportion of time with sensor glucose in target range (5.6 to 10.0mmol/L)

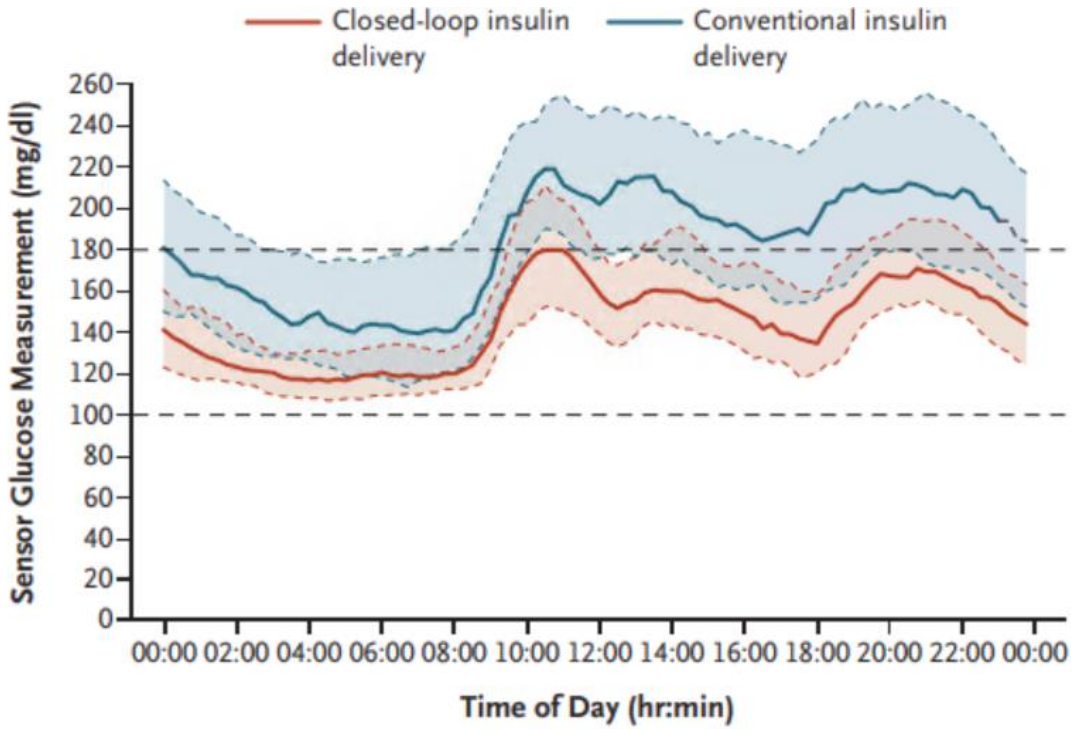
Bally et al. N Engl J Med. 2018

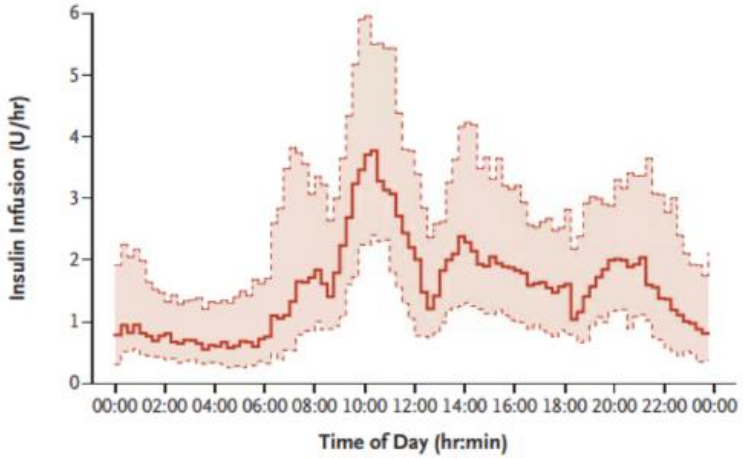
- Parallel design, two centre study
- 136 inpatients with type 2 diabetes or hyperglycaemia requiring insulin

Results

Fully closed-loop was safe and associated with:

- ↑ TIR (5.6-10.0mmol/L) – 66% v 42%
- ↓ time in hyperglycaemia – 24% v 50%
- ↓ Mean glucose 8.6mmol/L v 10.4 mmol/L
- NO increased risk of hypoglycaemia

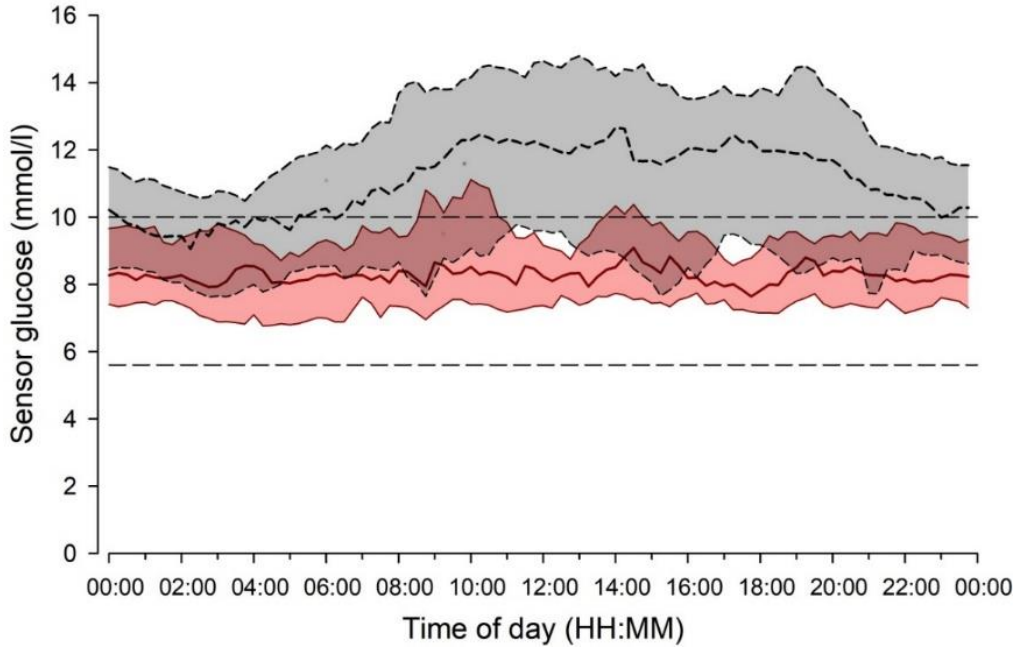




6 additional hours each day with glucose in target range

Bally et al. N Engl J Med. 2018

- Parallel design, two centre study
- 43 inpatients with type 2 diabetes or hyperglycaemia requiring insulin **receiving nutritional support**
- Fully closed-loop v usual SC insulin therapy



Results

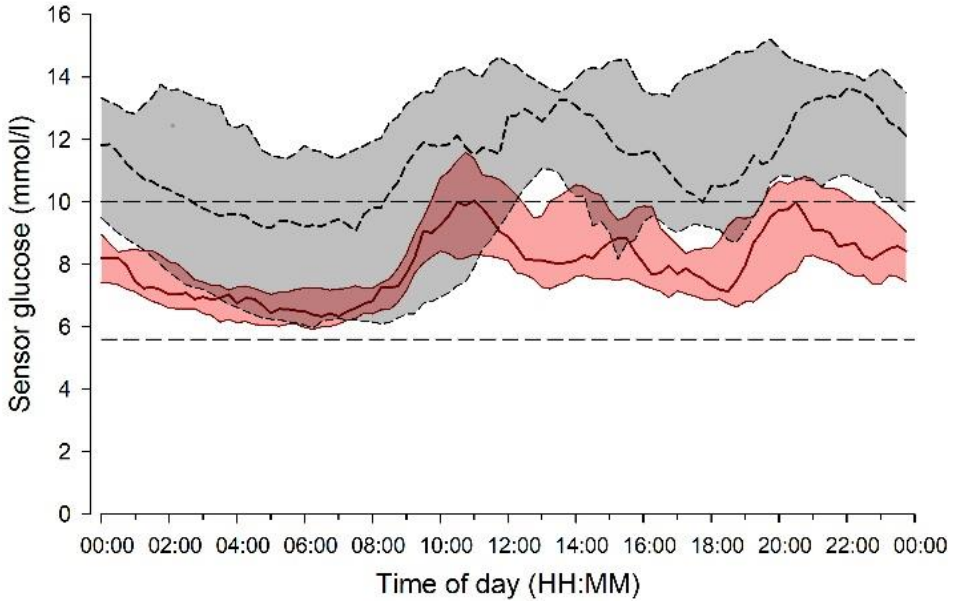
Fully closed-loop was safe and associated with:

- ↑ TIR (5.6-10.0mmol/L) – 68% v 36%
- ↓ time in hyperglycaemia – 22% v 55%
- ↓ Mean glucose 8.5 mmol/L v 11.4mmol/L
- NO increased risk of hypoglycaemia

8 additional hours each day with glucose in target range

Boughton et al. Lancet D&E. 2019

- Retrospective subgroup analysis
- 17 inpatients with type 2 diabetes or hyperglycaemia requiring insulin **requiring haemodialysis**
- Fully closed-loop v usual SC insulin therapy



Results

Fully closed-loop was safe and associated with:

- ↑ TIR (5.6-10.0mmol/L) – 69% v 32%
- ↓ time in hyperglycaemia – 20% v 57%
- ↓ Mean glucose 8.1mmol/L v 11.0mmol/L
- NO increased risk of hypoglycaemia

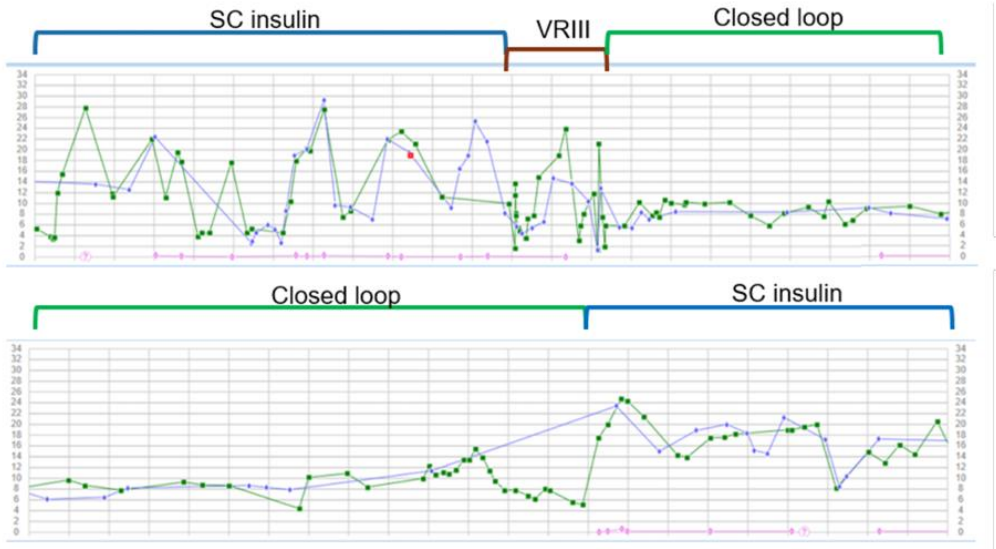
9 additional hours each day with glucose in target range

Bally et al. Kidney Int. 2019

Implementation

32 inpatients (mean age 61 years, 8 females, 24 males) with complex needs used fully closed-loop during admission, across medical and surgical wards.

- TIR (3.9 to 10.0mmol/L) – 53%
- Time in hyperglycaemia – 46%
- Mean glucose – 10.7mmol/L
- Time with glucose <3.9 mmol/L - 0.38%
- No episodes of severe hypoglycaemia or diabetic ketoacidosis.



Boughton et al. Diabet Med. 2023

Conclusions

Fully closed-loop is safe and effective at **improving glucose control in inpatients** requiring insulin (additional 6-9 hrs/day in target) compared to usual care **without increasing hypoglycaemia**.

Small implementation study suggests this technology is **readily translatable** into a real-world setting with the potential to transform the way inpatient diabetes is managed in the hospital.

Data from implementation projects aims to provide real-world evidence of clinical benefits across a more heterogeneous patient group in different hospital systems to support adoption and reimbursement.

Content

- Fully closed-loop in the **inpatient setting**
- Closed-loop for people with **type 2 diabetes**
- Closed-loop for people with **cystic fibrosis related diabetes**

Background

- **Growing population** with T2D globally and longer duration of disease due to earlier age at diagnosis.
  - 15% of people with T2D use insulin but clinical need likely much higher.
- Intensive glycaemic management to achieve target HbA1c is supported by good-quality evidence but >50% of people with T2D do not meet recommended glycaemic targets due to:
  - **therapeutic inertia** and healthcare professional workload
  - **risk of hypoglycaemia** with standard insulin therapy
- Day to day **variability in insulin requirements** in outpatients with T2D is **very high**; even higher than in adults with T1D - CV of daily insulin requirements 38% vs. 17%.

Lakshman R et al Diabetes Technol Ther. 2023

CamAPS HX FULLY closed-loop

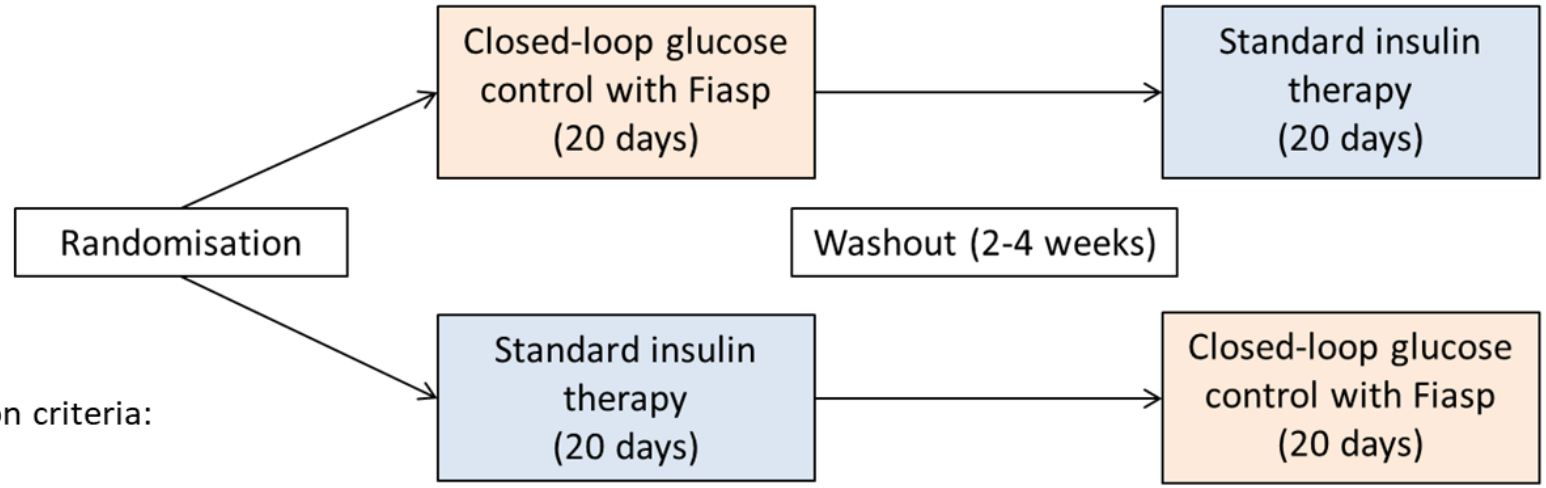
Features

- **Fully automated** - no requirement for meal-time bolusing
- Adaptive algorithm
- Adjustable target glucose level
- Boost / Ease off
- Optional correction bolusing
- Customizable alarms for hypo- and hyperglycaemia
- Remote review capability via Glooko
- Approved for quick acting and ultra-rapid acting insulins

Android smartphone hosting CamAPS HX

Closed-loop to manage OUTPATIENT type 2 diabetes: AP-Renal study

Open-label, two-centre, multinational (UK and Switzerland), randomised, two-period crossover design



Key inclusion criteria:

- Adults
- Type 2 diabetes
- Insulin therapy
- ESRD requiring dialysis (HD or PD)

*During standard insulin therapy participants wore a masked glucose sensor

Primary endpoint: Proportion of time with sensor glucose in target range (5.6 -10.0mmol/L)

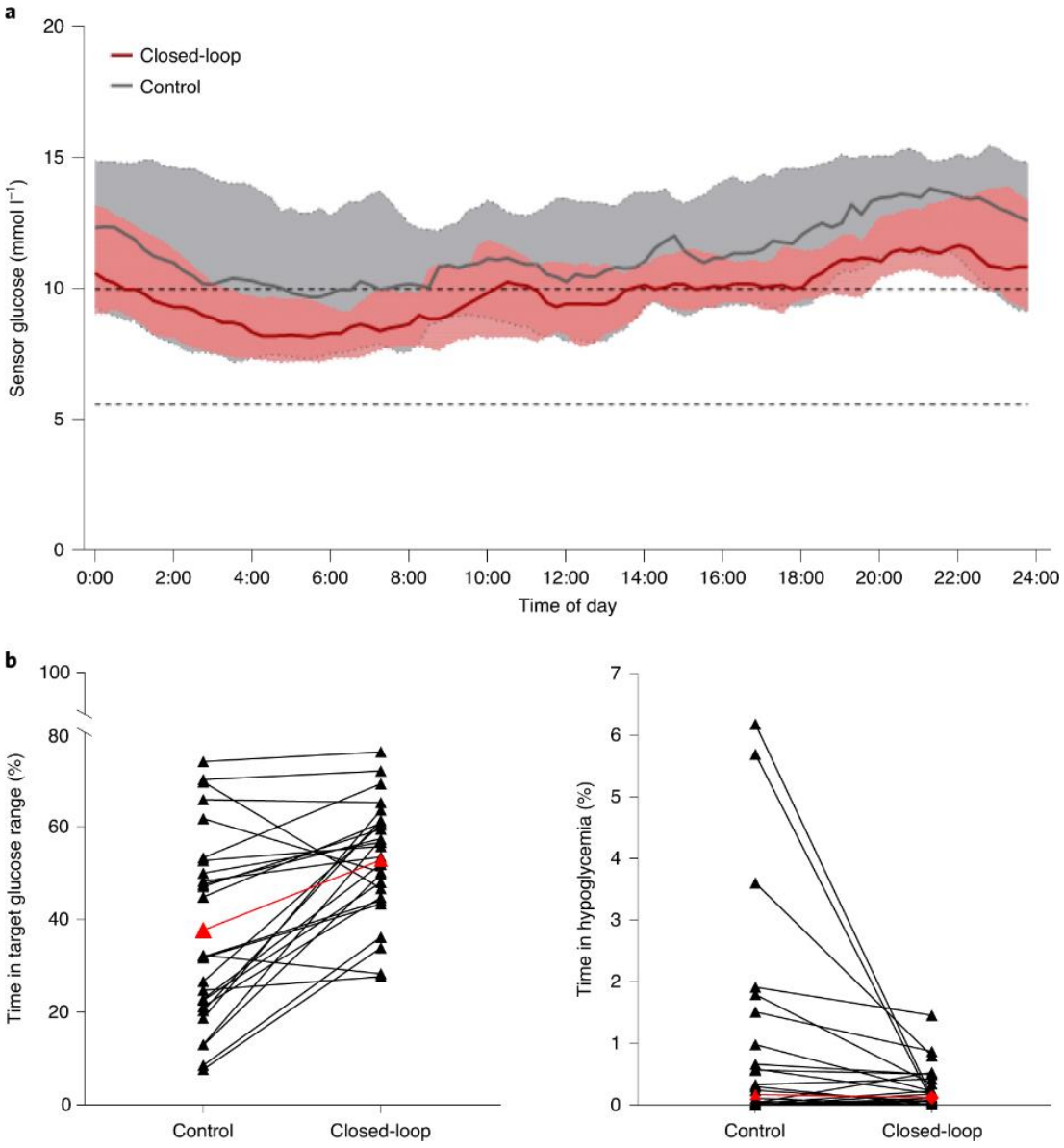
Boughton et al. Nature Med. 2021

- 26 outpatients with type 2 diabetes requiring insulin and ESRD requiring dialysis
- Fully closed-loop v usual SC insulin therapy

Results

Fully closed-loop was safe and associated with:

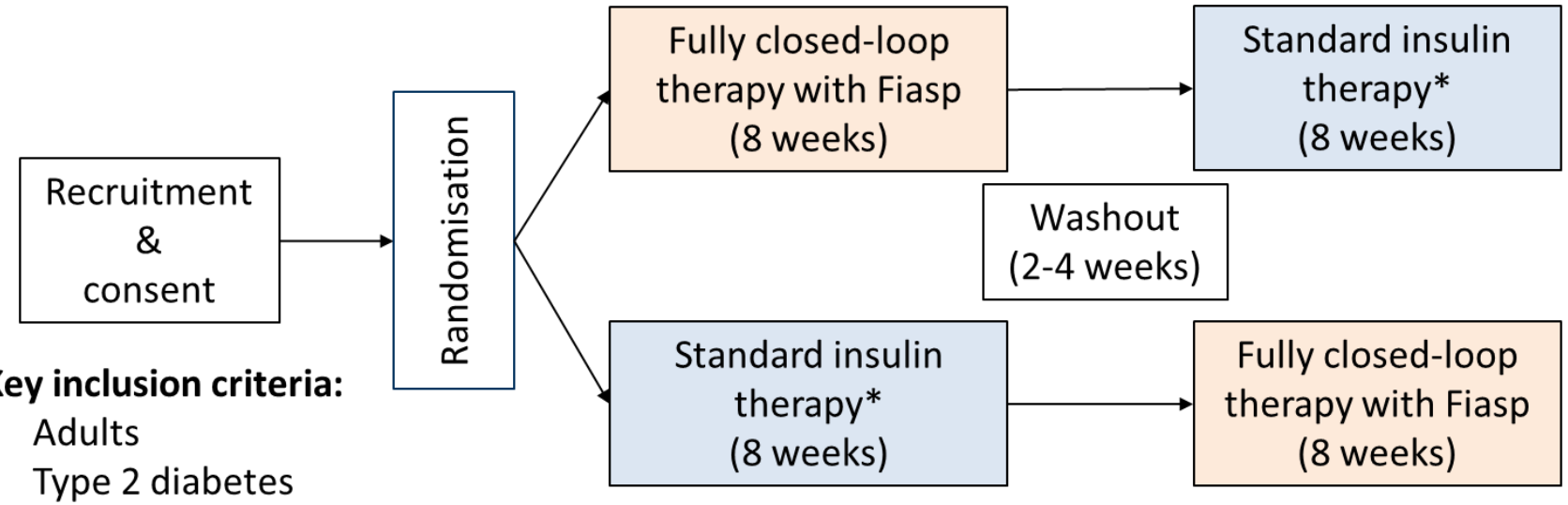
- ↑ TIR (5.6-10.0mmol/L) – 53% v 38%
- ↓ time in hyperglycaemia – 43% v 57%
- ↓ Mean glucose – 10.1mmol/L v 11.6mmol/L
- ↓ time in hypoglycaemia - 0.1% v 0.2%



3.5 additional hours each day with glucose in target range

Closed-loop to manage OUTPATIENT type 2 diabetes

Open-label, single-centre (Cambridge, UK) randomised, two-period crossover design



Key inclusion criteria:

- Adults
- Type 2 diabetes
- Insulin therapy

*During standard insulin therapy participants wore a masked glucose sensor

Primary endpoint: Proportion of time with sensor glucose in target range (3.9 – 10.0mmol/L)

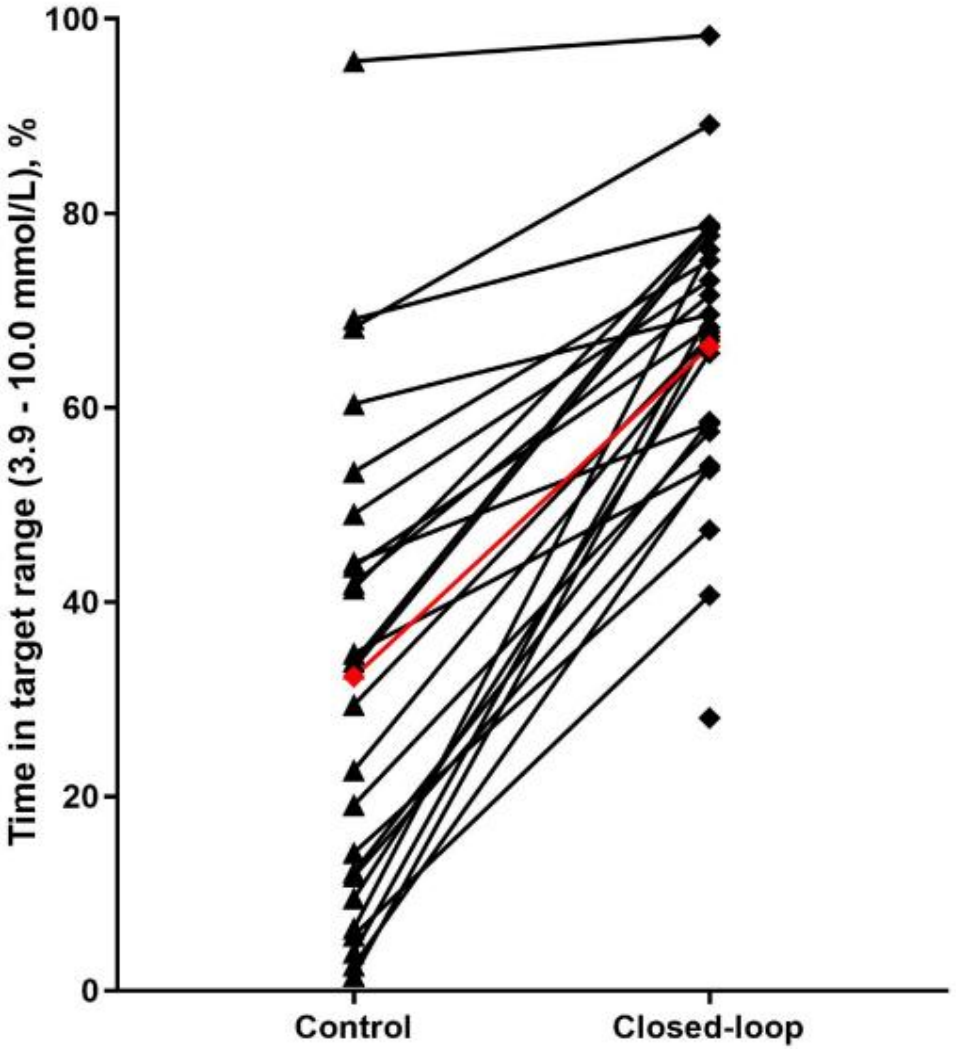
Daly et al. Nature Med. 2023

- 26 outpatients with type 2 diabetes requiring insulin
- Baseline HbA1c - 9.0% (75mmol/mol)
- Fully closed-loop v usual SC insulin therapy

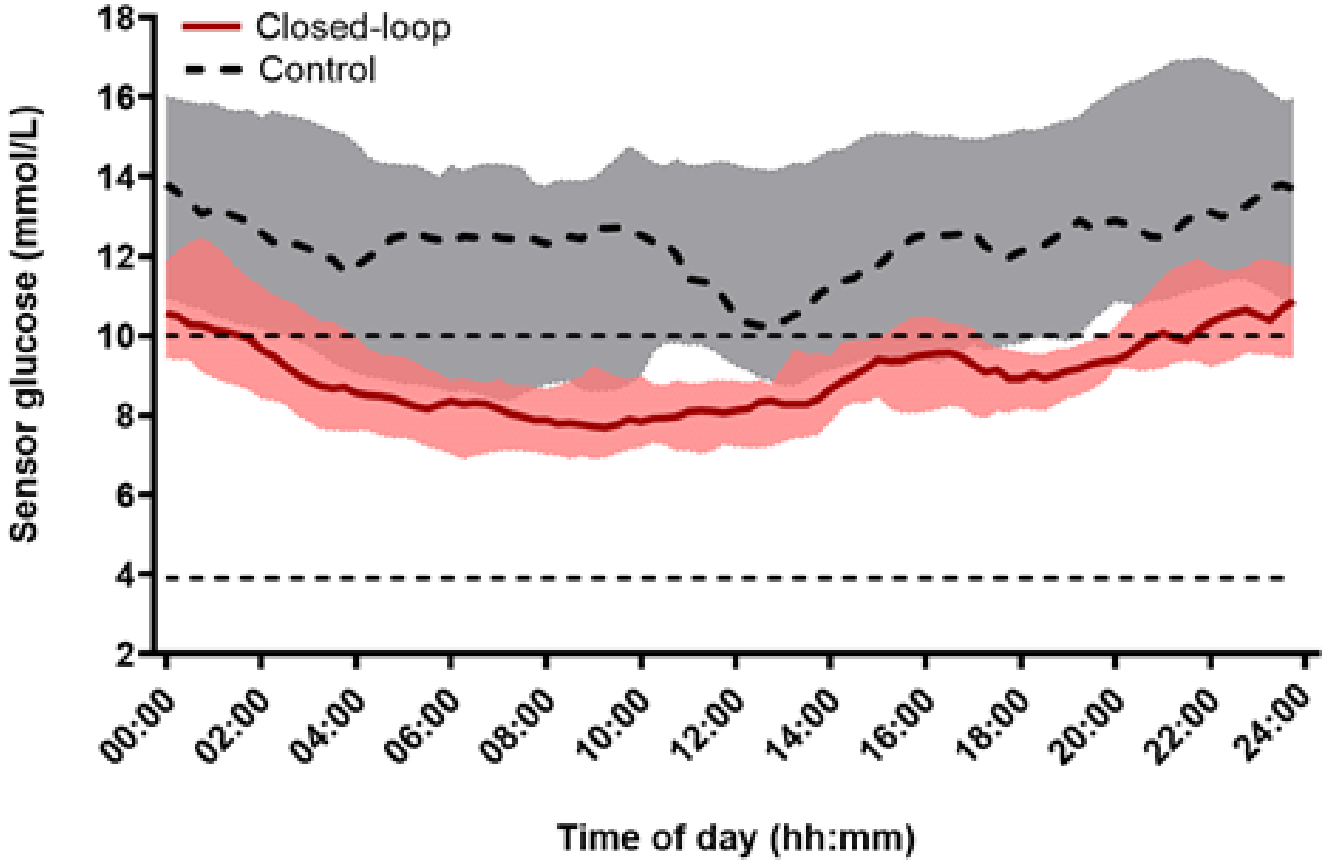
Results

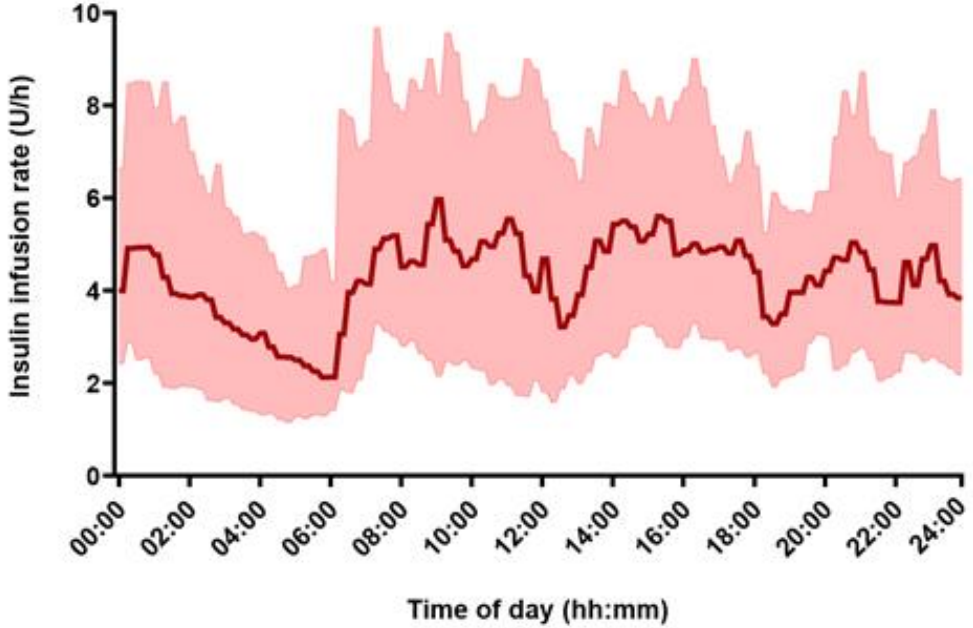
Fully closed-loop was safe and associated with:

- ↑ TIR (3.9 -10.0mmol/L) – 66% v 32%
- ↓ time in hyperglycaemia – 33% v 67%
- ↓ Mean glucose – 9.2mmol/L v 12.6mmol/L
- ↓ HbA1c – 7.3% v 8.7% (57 v 72mmol/mol)
- NO increased risk of hypoglycaemia



8 additional hours each day with glucose in target range


Closed-loop
Control
Sensor glucose (mmol/L)
18
16
14
12
10
8
6
4
2
00:00
02:00
04:00
06:00
08:00
10:00
12:00
14:00
16:00
18:00
20:00
22:00
24:00
Time of day (hh:mm)


Insulin infusion rate (U/h)
10
8
6
4
2
0
00:00
02:00
04:00
06:00
08:00
10:00
12:00
14:00
16:00
18:00
20:00
22:00
24:00
Time of day (hh:mm)

Safety analysis

	Overall (n=26)	Closed-loop (n=26)	Control (n=25)
Number of severe hypoglycaemic events	0	0	0
Number of serious adverse events	8	4	2
Study related	1	1	0
Non study related	7	3	2
Number (%) of participants with serious adverse events	6 (23)	3 (12)	1 (4)
Number of other adverse events	11	5	5
Number (%) of participants with adverse events	11 (42)	5 (19)	5 (20)
Number of device deficiencies	6	6	0
Pump related	4	4	0
Sensor related	1	1	0
Smartphone related	1	1	0
Number (%) of participants with device deficiencies	5 (19)	5 (19)	0 (0)

What did you like about the closed-loop system?

- **Not having to fingerprick**
- Looking at the glucose levels as often as I did. Alarms telling me my blood sugar is high or low.
- **Not injecting** myself all the time
- Knowing I could **carry on with my lifestyle without worrying** about my blood sugars as I could check them anytime without the fuss of glucose testing and knowing insulin would be dispensed accordingly.
- A lot **better control** of my glucose levels and reduction in HbA1c
- I was **confident** to manage much **tighter control** keeping under 7mmol/L most of the time. It made it possible to take part in strenuous activity without keeping glucose high in fear of hypo. **It gave freedom**. Just brilliant
- Better control of insulin. **Adjusting my eating habits** as could see what raises levels. Peace of mind of sugar levels. Not having to remember to take insulin.
- The fact it did the thinking for me
- I liked **how easy it was to use** once I had all the information on its use.
- A complete **life changer.**
- It would **make my life so much better** and wonderful, and my family would agree

What are the things you did not like about the system?

- **Refilling the insulin pump** and having to make sure I had all the equipment to do so if I was away from home
- Sometimes tubing caught on kitchen drawers
- Being **attached to the pump all the time**. Having to be careful not to pull the cannula out.
- Refilling with insulin **every 3-4 days**
- I thought that every 3 days was a little too often to change the insulin
- Pump **disconnection from app. Bluetooth issues**. Short battery life of pump.
- The batteries on the pump not lasting and on two occasions dropping to low glucose levels
- Dropping out of transmitter to app. The pump and phone **lost connection** often and figuring out how to correct pump errors.
- **Connectivity problems** between sensor and phone.
- Risk of hypos at night if communication to pump fails..
- Waking up feeling low in the early morning or **being woken up by the system telling me I'm low.**

Conclusions

Closed-loop **improved glucose control** (additional 8 hrs/day in target) without increasing **hypoglycaemia** in adults with type 2 diabetes.

Closed-loop was **safe** and associated with very low time in hypoglycaemia.

Closed-loop devices were **manageable by users new to diabetes technologies** with high acceptability (92% auto mode use).

Fully closed-loop removes the need for any healthcare professional input for dose adjustment after initial training mitigating therapeutic inertia.

COYOTE Study

Multicentre, multinational randomised controlled trial in UK and Europe aims to demonstrate benefits within a larger, more heterogeneous patient group and provide data to **support adoption and reimbursement** (primary endpoint HbA1c).

- This will also provide data (including on potential complications e.g. kidney function, lipids etc.) for health economics to inform payers.
- Use of CGM in control arm will allow more rapid adoption of fully closed-loop due to glycaemic benefits of closed-loop above CGM+MDI.

Clincialtrials.gov: NCT06579404

Hybrid closed-loop for people with T2D

- 17 adults with T2D using insulin pumps
- Baseline HbA1c – 7.9% (63mmol/mol)
- Crossover RCT: Hybrid closed-loop (Diabeloop) v insulin pump + sensor for 12 weeks

Results

Hybrid closed-loop was safe and associated with:

- ↑ TIR (3.9 -10.0mmol/L) – 76% v 61%
- ↓ time in hyperglycaemia – 24% v 38%
- ↓ Mean glucose – 8.8mmol/L v 9.6mmol/L
- NO increased risk of hypoglycaemia

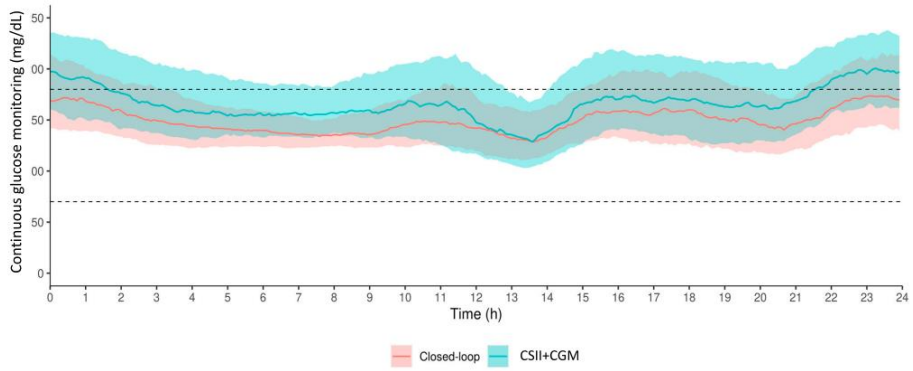


Figure 2—Glucose control during the closed-loop and the CSII + CGM periods. The shaded areas show the 95% CI.

3.6 additional hours each day with glucose in target range

Borel et al. Diabetes Care. 2024

Hybrid closed-loop for people with T2D

Non-randomised feasibility before and after studies:

- Control-IQ in basal-bolus and basal-only insulin users with T2D (n=30)
- Omnipod 5 in adults with T2D: from injections to hybrid closed-loop therapy

Glycaemic benefits observed but no control group

Real-world observations:

- Control-IQ in individuals with T2D transitioning from predictive low-glucose suspend (PLGS) to HCL (n=796)

Levy et al. Clinical Diabetes. 2023
David et al. Diabetes Care 2023
Fabris et al. JDST 2024

Content

- Fully closed-loop in the **inpatient setting**
- Closed-loop for people with **type 2 diabetes**
- Closed-loop for people with **cystic fibrosis related diabetes**

Background

- CFRD is the commonest comorbidity in CF
  - affects 15-20% of adolescents & 35-50% of adults
  - associated with decline in lung function, compromised nutritional status, and earlier mortality
- Recommended management is insulin therapy:
  - ↓ risk of pulmonary infections
  - improvements in nutritional status and lung function
- Insulin adds to burden of CF self-management. Reducing treatment burden was the **top research priority** in the James Lind Alliance Priority Setting Partnership in CF

Why closed-loop?

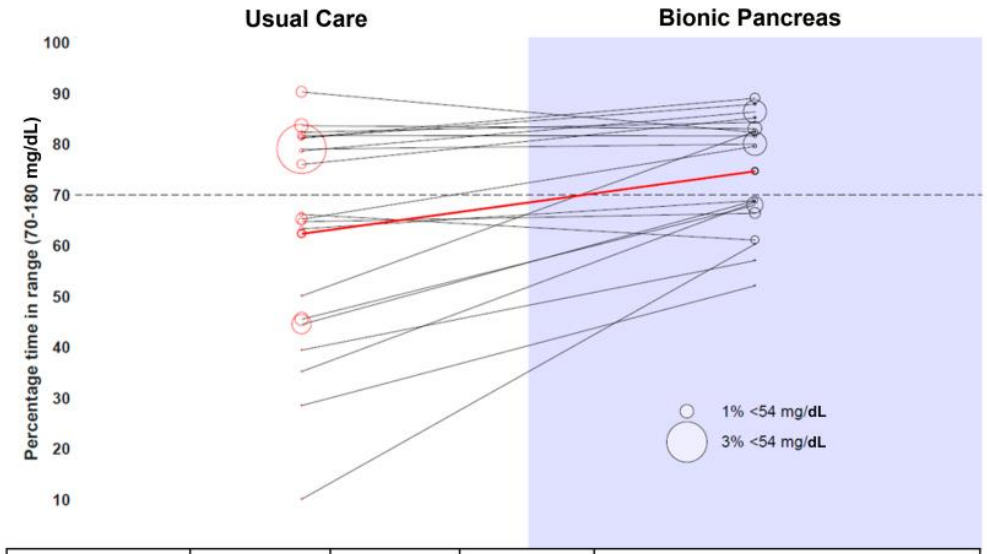
Potential to:

- Manage **high variability in day-to-day insulin needs** due to pulmonary infections, use of corticosteroids, exocrine pancreas insufficiency and use of nutrition support.
- **Reduce burden** of self-management.

Glucose control increasingly important with increased life expectancy → longer duration with diabetes and greater risk of complications (retinopathy, nephropathy)

Hybrid closed-loop for people with CFRD

- 20 adults with CFRD
- Baseline HbA1c – 7.4% (57mmol/mol)
- Crossover RCT: Hybrid closed-loop (iLet) v usual care (50% MDI, 50% pumps) for 2 weeks



	UC	BP	P-value	Estimated Treatment Difference
Mean % TIR	63 (22)	75 (11)	0.001	12 (95% CI 5–19%)

Results

Hybrid closed-loop was safe and associated with:

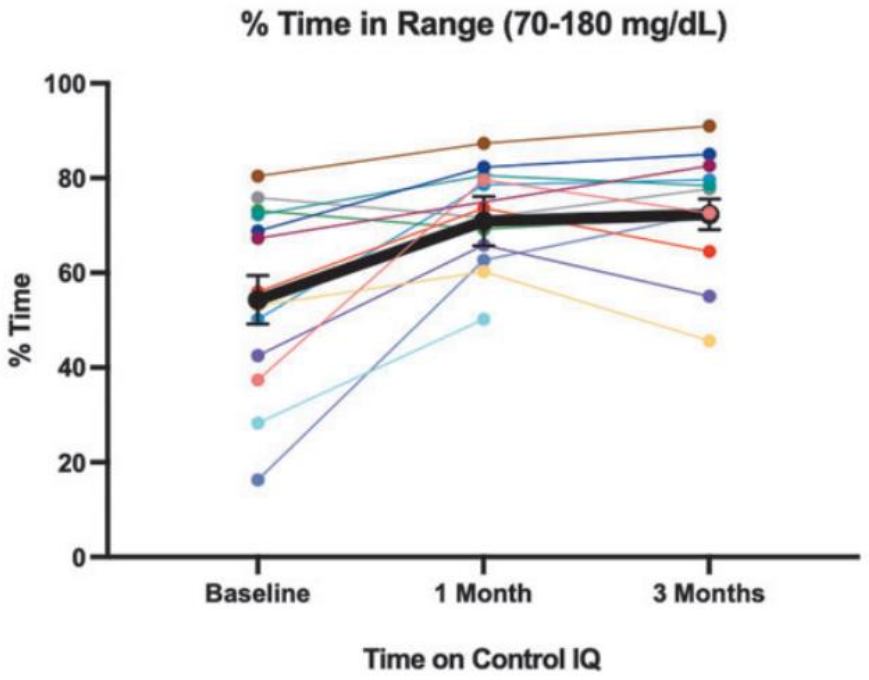
- ↑ TIR (3.9 -10.0mmol/L) – 75% v 62%
- ↓ time in hyperglycaemia – 18% v 31%
- ↓ Mean glucose – 8.3mmol/L v 9.5mmol/L
- NO increased risk of hypoglycaemia

2.9 additional hours each day with glucose in target range

Sherwood et al. Diabetes Care. 2023

Hybrid closed-loop for people with CFRD

Retrospective study of 13 adolescents and adults with CFRD using Control IQ for 3 months



Scully et al. Diabetes Technol Ther. 2022

CL4P-CF Study

An open-label, multi-centre, randomised, two arm single period parallel study to assess the **efficacy, safety and utility** of hybrid closed-loop glucose control compared to standard insulin therapy combined with continuous glucose monitoring in young people (≥16 years) and adults with CFRD.

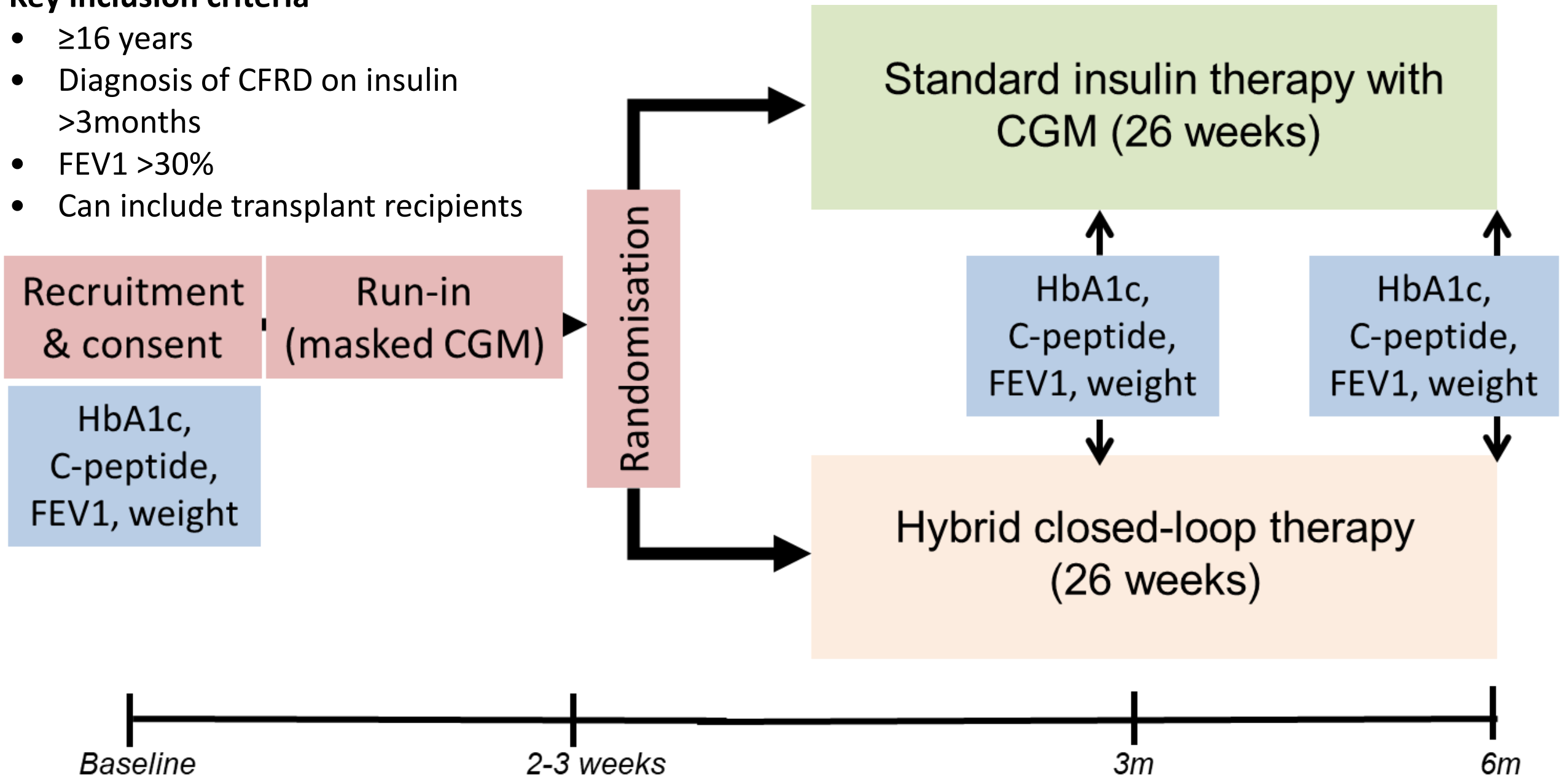
Aiming for **114 randomised participants** (recruitment will target up to 128 participants to allow for drop-outs).

NIHR | National Institute for Health and Care Research

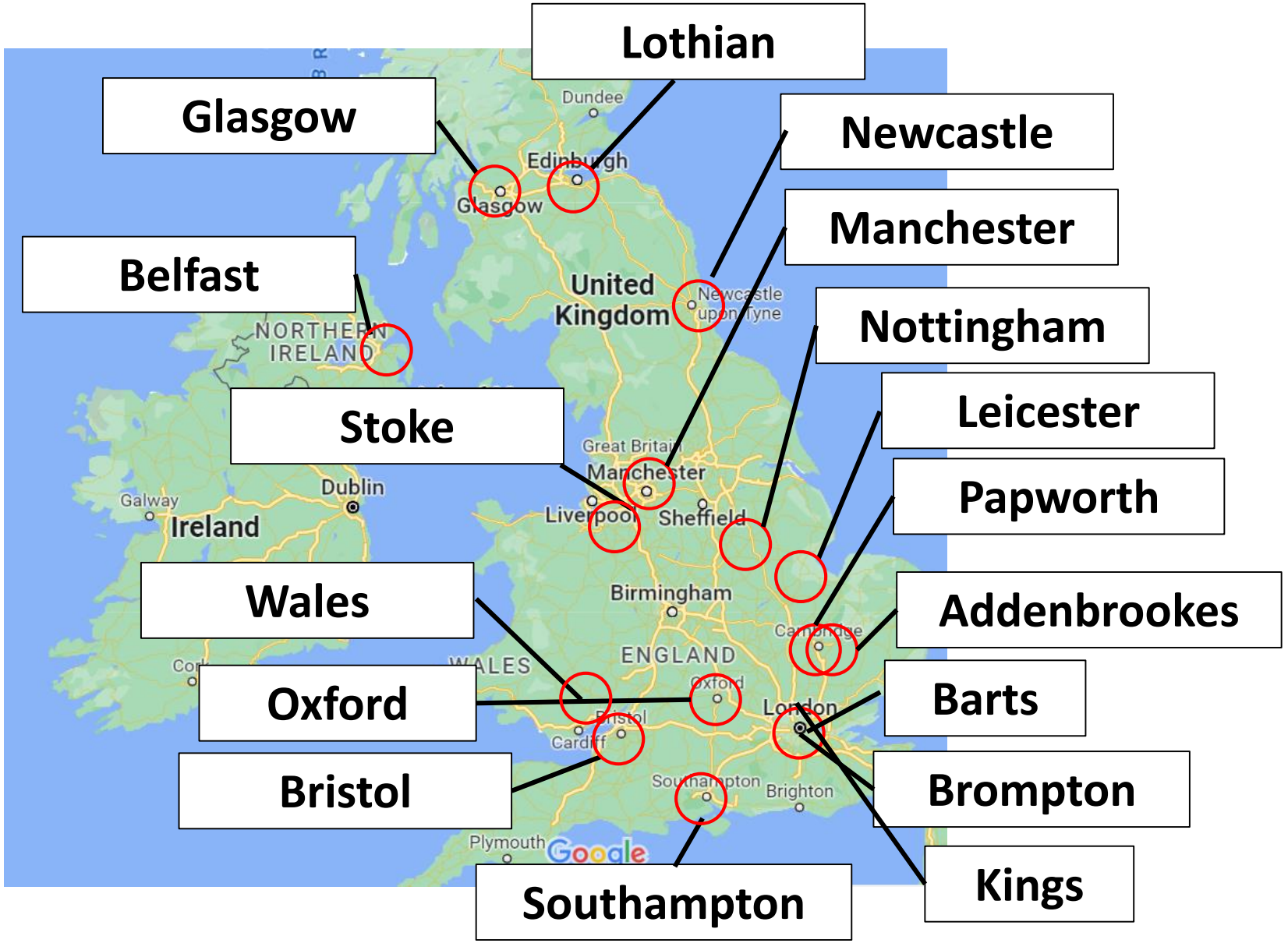
Cystic Fibrosis Trust

Key inclusion criteria

- ≥16 years
- Diagnosis of CFRD on insulin >3months
- FEV1 >30%
- Can include transplant recipients



Sites



17 Clinical centres in the UK

Data management & statistics (Oxford Diabetes Trial Unit)

Central lab (Cambridge)

Qualitative assessment (Edinburgh)

CamAPS FX hybrid closed-loop

Dexcom G6 sensor

CamAPS FX app on Android smartphone

Ypsopump insulin pump

- **Adaptive algorithm**
- **Adjustable target glucose level**
- Boost / Ease off
- Customisable alarms for hypo & hyperglycaemia
- **Approved for quick acting & ultra-rapid acting insulins**
- Communication via Bluetooth
- Real time data upload to Glooko cloud

Endpoints

Primary endpoint: Time in target glucose range (3.9 to 10.0 mmol/l) over 26 weeks

Secondary endpoints

Efficacy:

- Glycaemic control (time in hyper/hypoglycaemia, mean glucose, glucose variability, time in tight range, HbA1c)
- Total daily insulin dose and fasting C-peptide
- Weight and BMI
- FEV1, frequency of pulmonary exacerbations and hospitalisations

Safety: severe hypoglycaemia and other adverse events

Utility and human factors: validated questionnaires and interviews

Case

- 34 yo female
- CFRD since 2008
- Completed DAFNE self-management education
- MDI (bolus only) and Freestyle Libre 2
- TDD 24 units/day
- HbA1c at baseline: 54 mmol/mol

Average Glucose

11.7 mmol/L

Standard Deviation

3.2 mmol/L

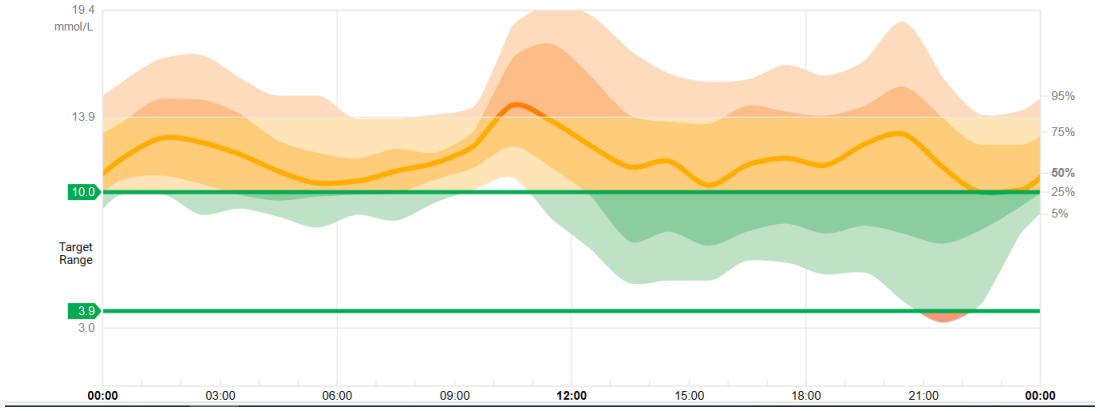
GMI

N/A

Time in Range

23% Very High
46% High
29% In Range
1% Low
<1% Very Low

Target Range:
3.9-10.0 mmol/L



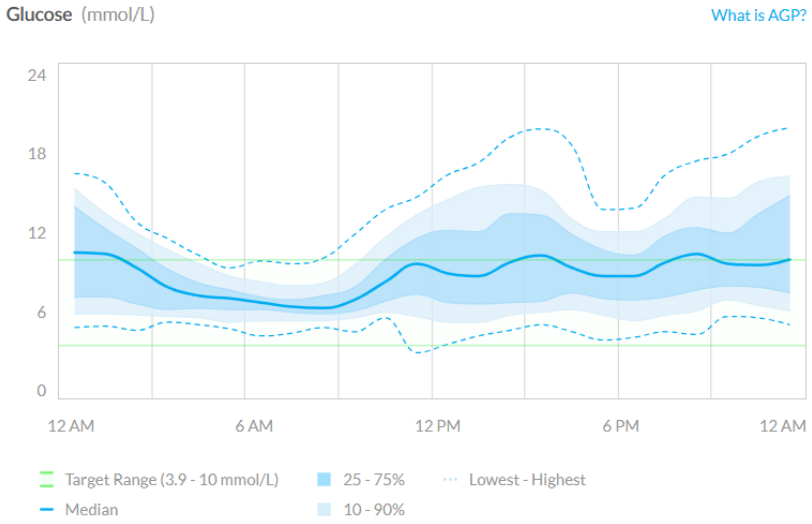
Randomised to hybrid closed-loop

Glucose (CGM)

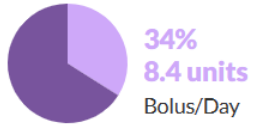
8%	Very High > 13.9 mmol/L
23%	High 10.1-13.9 mmol/L
69%	Target Range 3.9-10 mmol/L
0%	Low 3-3.8 mmol/L
0%	Very Low < 3 mmol/L

% Time CGM Active	96.1% (13.5 days)

GMI	7.2% (55.1 mmol/mol)
Average	9 mmol/L
SD	3 mmol/L
CV	33%
Median	8.2 mmol/L
Highest	19.5 mmol/L
Lowest	3.3 mmol/L



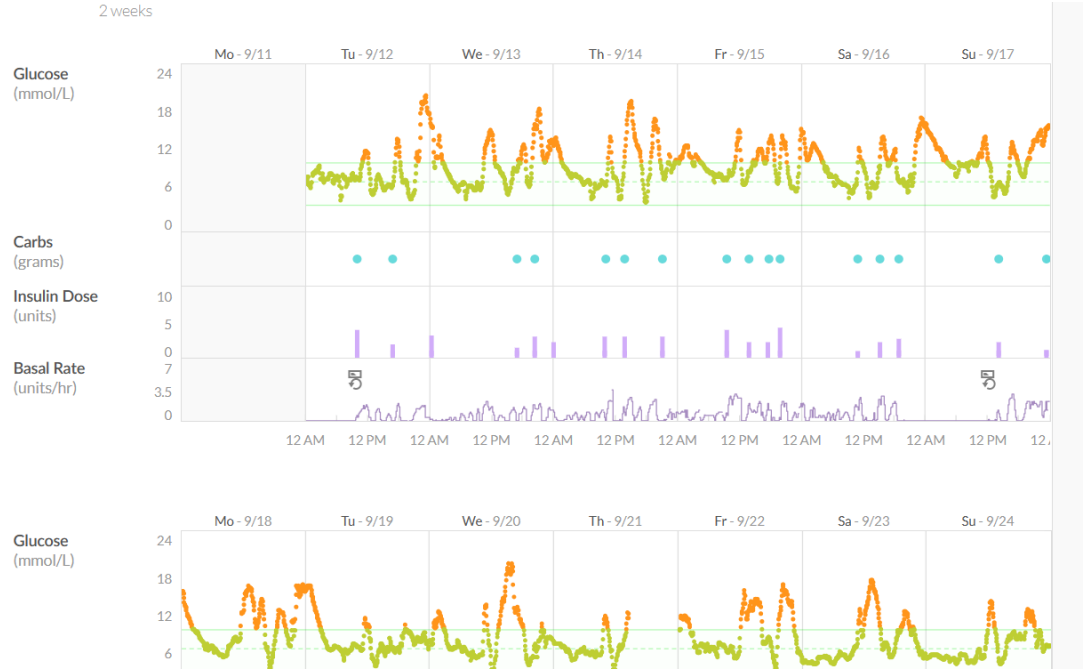
Insulin



Daily Dose	24.4 units
Overrides (%)	1.3% (1 boluses)
# Bolus/Day	5.6

HbA1c at 3 months: 44mmol/mol

TDD: 24.5 units/day

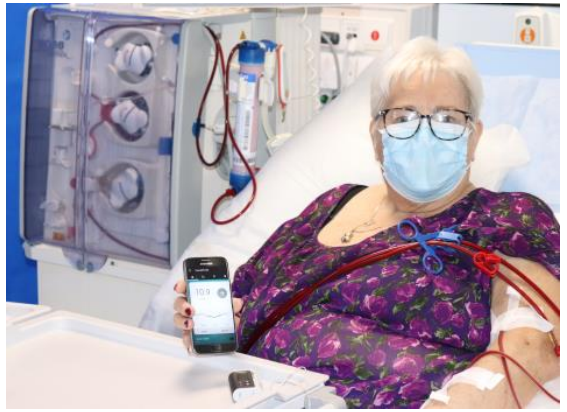


Conclusions

- CFRD is increasing in prevalence
- Current treatments are limited and burdensome
- Hybrid closed-loop has the potential to improve glucose control, reduce management burden and be translated rapidly into clinical practice.
- Large multicentre RCTs are required to establish efficacy and safety of the hybrid closed-loop approach in CFRD

Acknowledgements

Study participants:



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