UNIVERSITY OF CAMBRIDGE

Closed loop systems in diabetes – how close to routine clinical use?

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on behalf of Artificial Pancreas group

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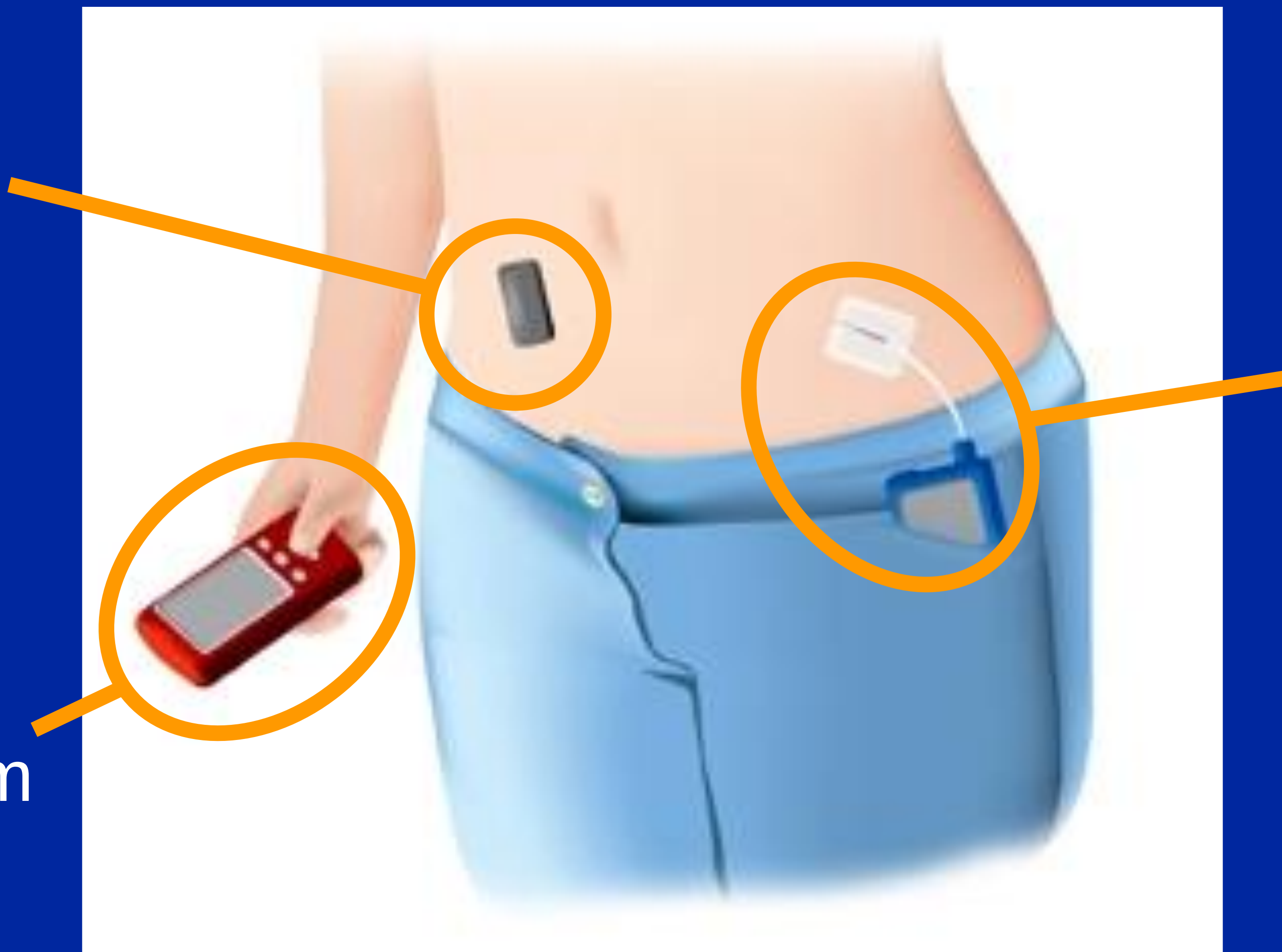
Duality of interest declaration

Advisory Panel:	Animas, Edwards Lifesciences, Eli Lilly
Research Support:	Minimed Medtronic, Abbott Diabetes Care, Animas, Edwards Lifesciences
Speaker's Bureau:	LifeScan, BBraun, Novo Nordisk, Eli Lilly
License fees:	Becton Dickinson, BBraun, Medtronic
Other:	Patent applications

The artificial pancreas



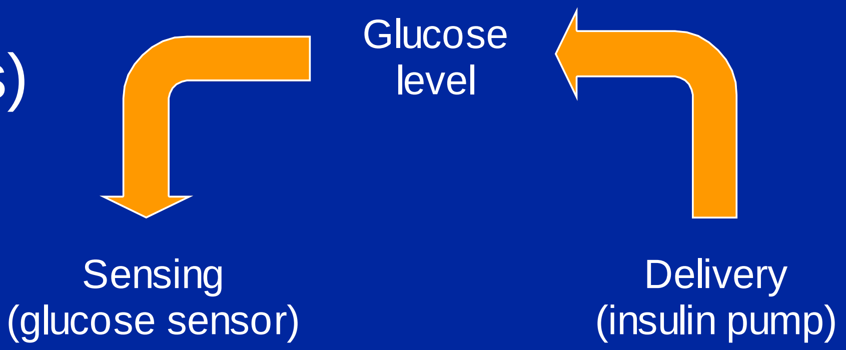
Content

- Introduction and challenges
- Home overnight closed loop in adolescents with type 1 diabetes
- Other home studies underway
- Use of closed loop outside type 1 diabetes

A bit of terminology …

- Open loop
  - Conventional therapy in type 1 diabetes
  - Insulin dosing based on 4-6 glucose measurements per day

- Closed-loop (Artificial Pancreas)
  - Insulin dosing titrated every 1 – 15 min

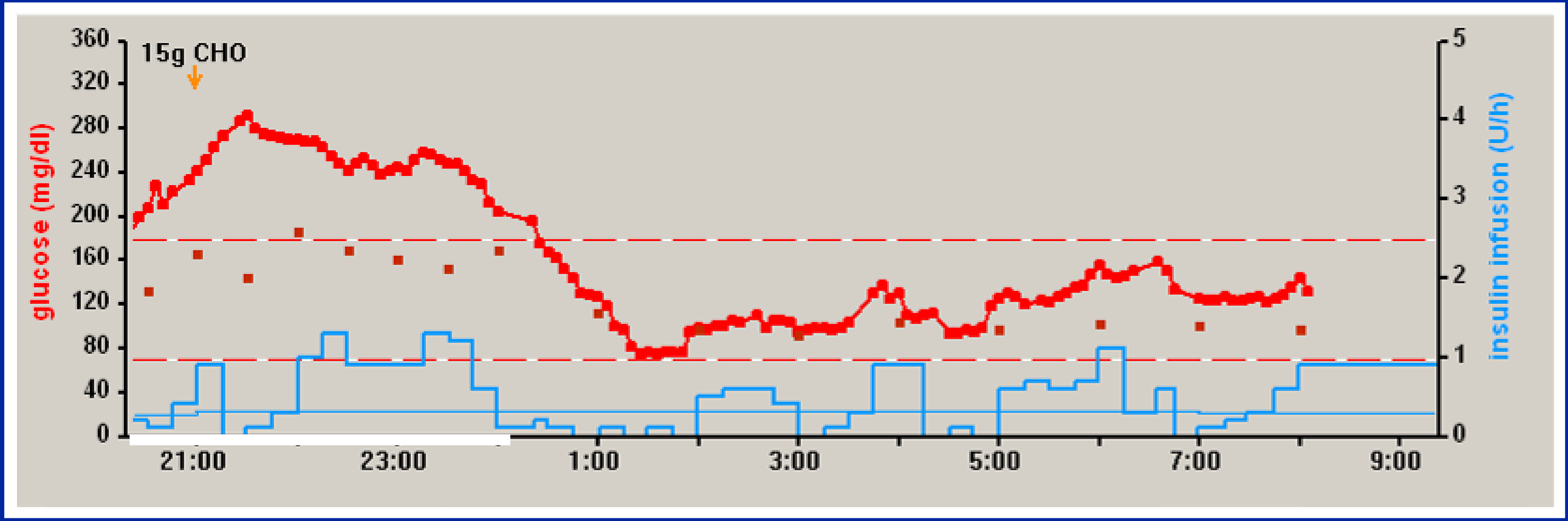


Accuracy and reliability of CGM devices

Minimed Paradigm Veo & Enhanced Enlite

Dexcom Gen4

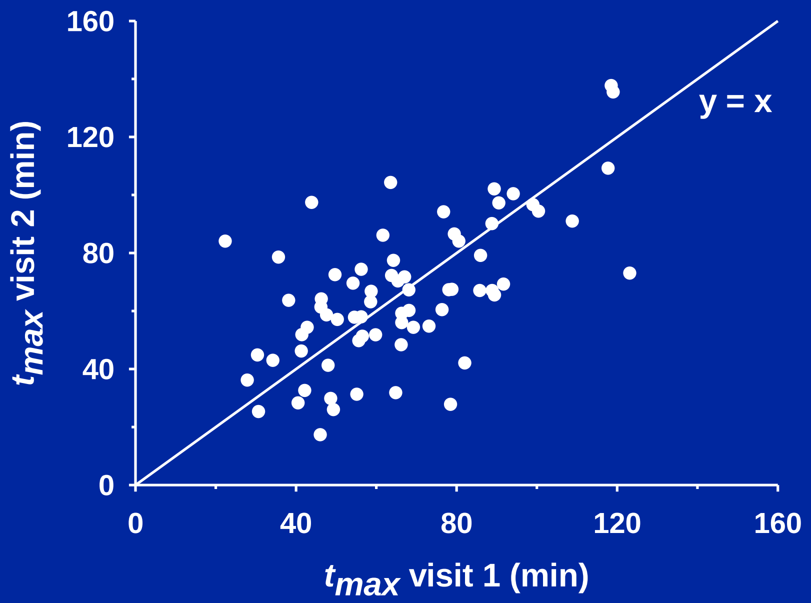
Freestyle Navigator II Abbott



Inter- and intra-subject variability: Aspart

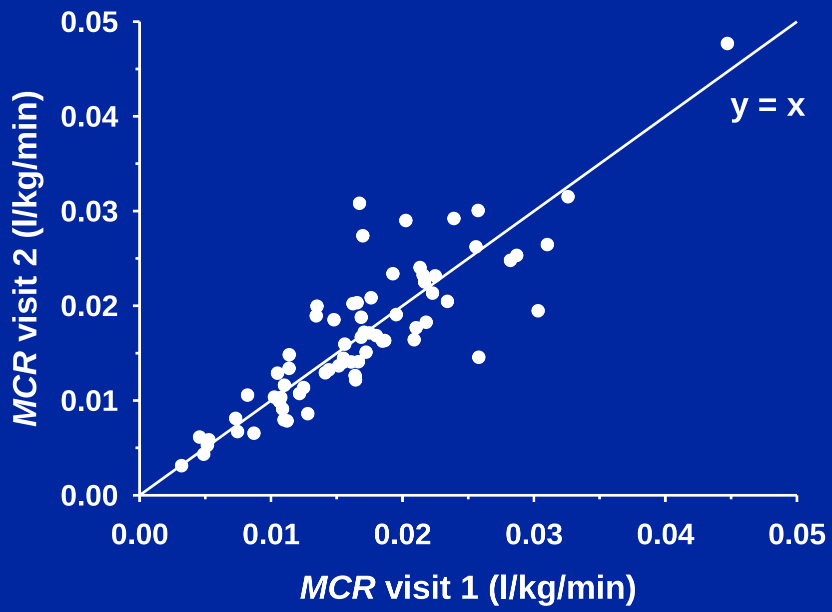
Time to maximum concentration

37% IOV out of total variance



Metabolic clearance rate

13% IOV out of total variance



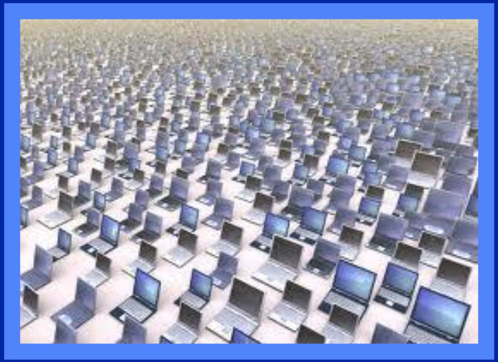
- Peak prandial insulin – low reproducibility
- Overnight insulin concentration by insulin pump – high reproducibility

Haidar *et al*, Diabetes Care 36, 2013

Benefits of closed-loop

- Low biological risk

- Scalability



- Innovation

5 years of clinical research centre studies

- Population:
  - 60 young people (6-18yrs)
  - 78 adults
  - 24 pregnant women
- 11 studies:
  - six overnight
  - three 24h
  - two 36h (adolescents)
- ~ 3,000 hours of closed-loop operation

Hovorka *et al, Lancet 375:* 2010
Hovorka *et al*, *BMJ 342* : 2011
Murphy *et al*, Diabetes Care 34: 2011
Murphy *et al,* Diabetes Care 34: 2011
Elleri *et al, Diabetes Care 36: 2013*

Rationale for Home Studies

Previous studies in clinical research facility demonstrated:

- Closed loop control is safe
- Improves glycaemic control
- Reduces risk of nocturnal hypoglycaemia

Closing the loop overnight in young people with type 1 diabetes in the home setting

Hovorka *et al, Diabetes Care 37:* 2014

Study objective

- To assess safety, efficacy, and utility of overnight closed loop *vs.* sensor augmented pump therapy in the home setting

Florence prototype

Navigator transmitter

Dana R insulin pump

Control algorithm device

Every 12 minutes

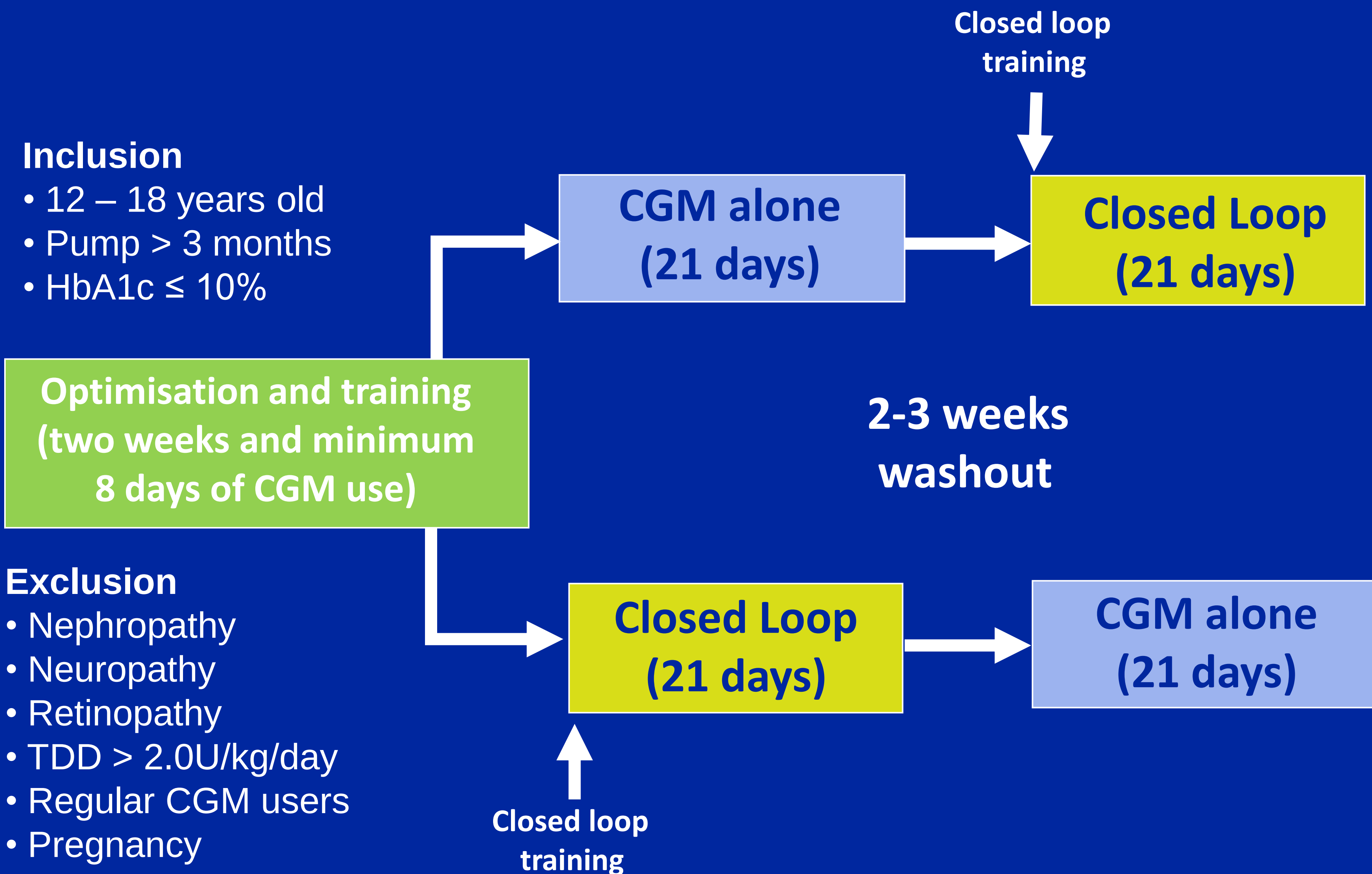
Companion receiver

Every 1 minute

Elleri *et al, Pediatr Diabetes 13:* 2012

Study Design

Inclusion
- 12 – 18 years old
- Pump > 3 months
- HbA1c ≤ 10%



Exclusion
- Nephropathy
- Neuropathy
- Retinopathy
- TDD > 2.0U/kg/day
- Regular CGM users
- Pregnancy

Baseline characteristics

	Youth T1D N = 16
Gender (M/F)	10/6
Age (yrs)	15.4 ± 2.0
BMI (kg/m^2)	21.7 ± 2.2
HbA1c (%)	8.0 ± 0.9
Duration of diabetes (yrs)	7.2 (4.3)
Duration on pump (yrs)	3.0 (2.3)
Total daily insulin dose (U/day)	54.9 (18.0)

System details

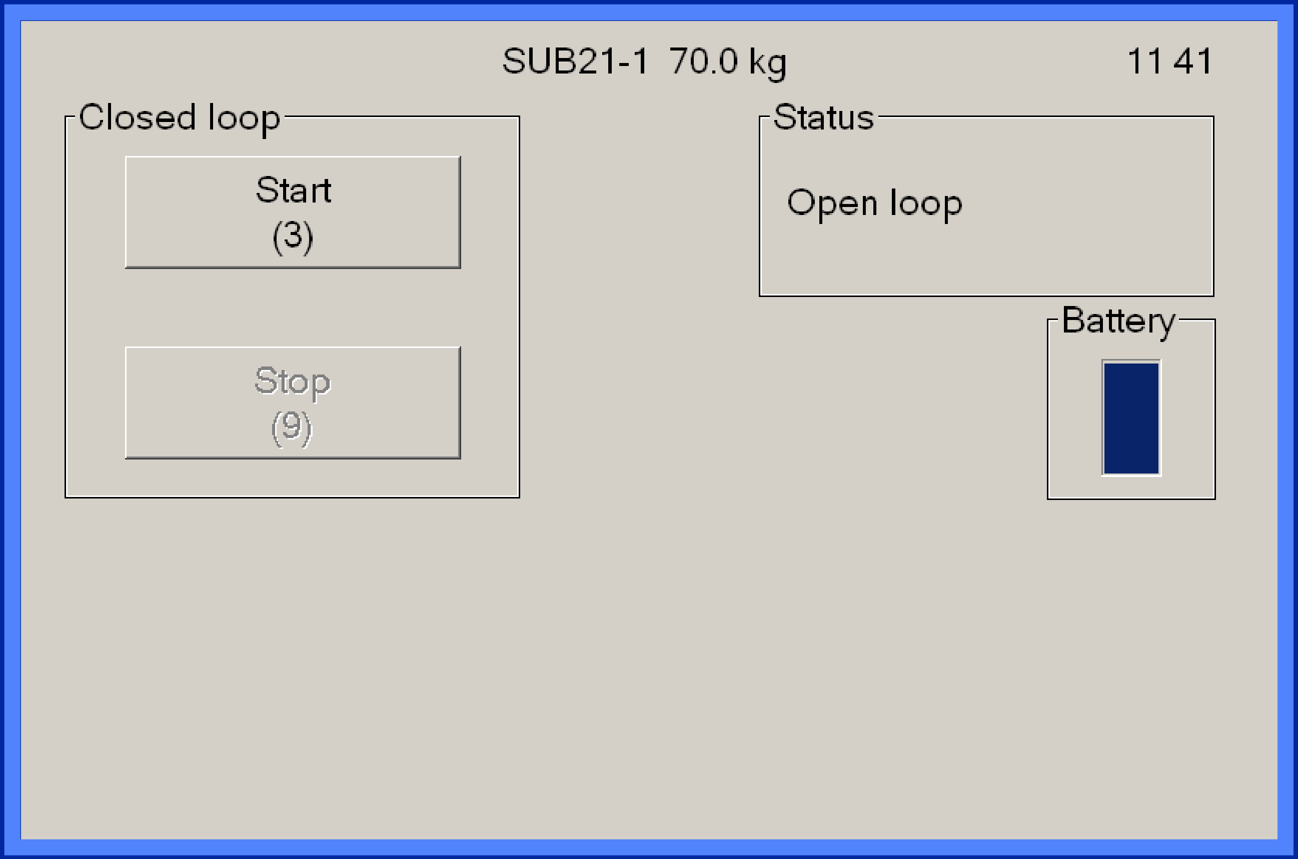
- Control algorithm
  - Adaptive model predictive control
  - Manual prandial boluses
  - Initialised by body weight, TDD, and basal pump settings
- No remote monitoring
- Troubleshooting by participants
- 24 hour support line

- Safety features
  - Calibration check prior to start of closed loop
  - Fallback to pre-programmed basal pump rate

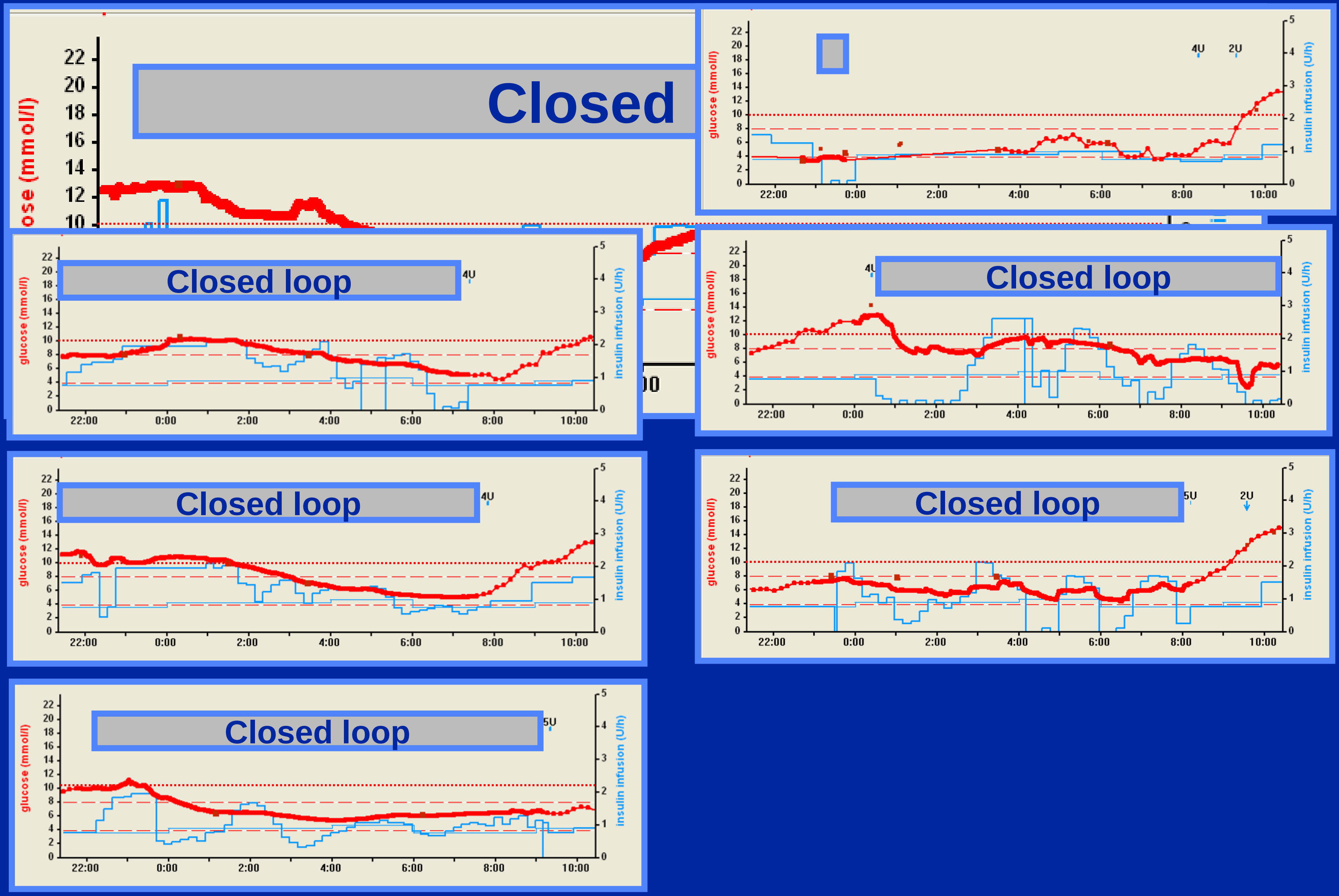
    - on sensor data unavailability

    - lack of pump connectivity
  - Maximum insulin infusion
  - Safety supervisor

Main screen


SUB21-1 70.0 kg
11 41
Closed loop
Start
(3)
Stop
(9)
Status
Open loop
Battery

Adolescent - week of closed loop



Results

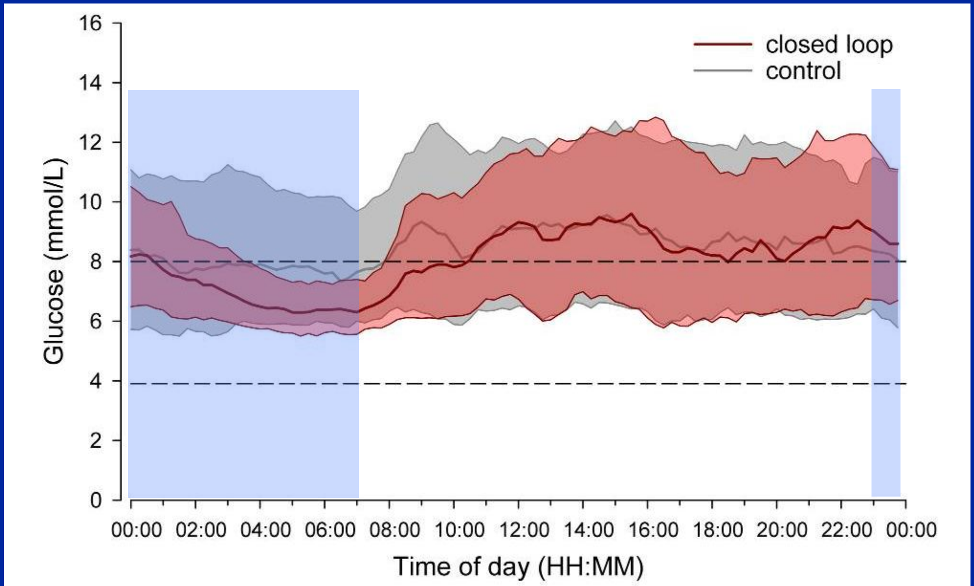
From 23:00 to 07:00

	Closed loop N = 16	Control N = 16	P
Number of evaluable nights	269	282	
*Time in target 3.9–8.0mmol/l (%)	64 (45-79)	47 (18-70)	<0.001
Time in target 3.9–8.0mmol/l (%)	68 (43-86)	46 (13-77)	<0.001
Mean glucose (mmol/l)	7.6 (1.8)	8.4 (2.9)	<0.001
Time in target 3.9–10.0mmol/l (%)	85 (68-94)	69 (42-87)	<0.001
Time < 3.9mmol/l (%)	1.4 (0.4 – 5.0)	0.9 (0.0 – 9.7)	0.13
Time > 8.0mmol/l (%)	30 (16-52)	43 (15-82)	<0.001
Nights glucose <3.5mmol/l (%)	10	17	0.01

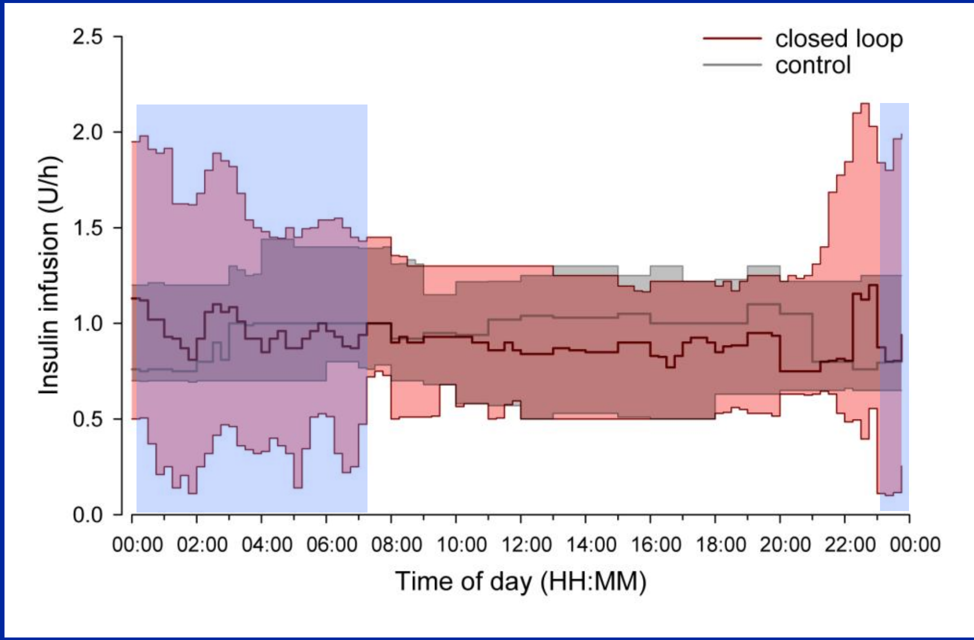
*Adjusted for simultaneous use of sensor to control insulin delivery and assess outcome

Results

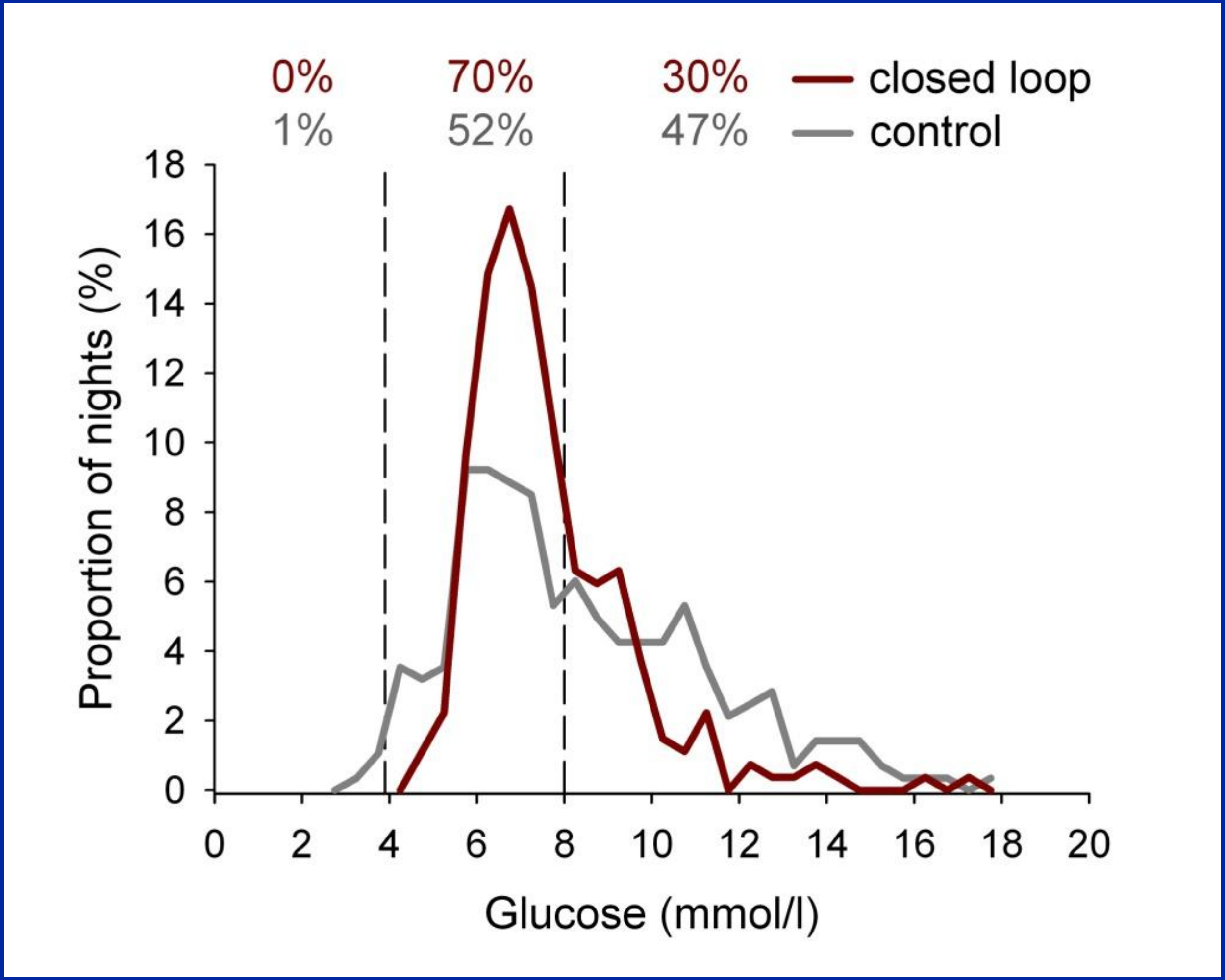
Sensor glucose



Insulin delivery



Mean overnight glucose



Other outcomes

	Closed loop N = 16	Control N = 16	P
24h mean glucose (mmol/l)	8.5 (1.7)	9.0 (2.2)	0.006
24h time in 3.9–10.0mmol/l (%)	70 (58-79)	60 (46-73)	<0.001
Night insulin delivery (U)	8.1 (6.5-10.8)	7.2 (5.8 to 9.1)	<0.001
Total daily boluses (U)	25.3 (19.8-33.0)	28.7 (22.0-36.4)	<0.001
Total daily dose (U)	49.9 (39.6-61.9)	53.2 (42.5-61.7)	0.009

Safety evaluation

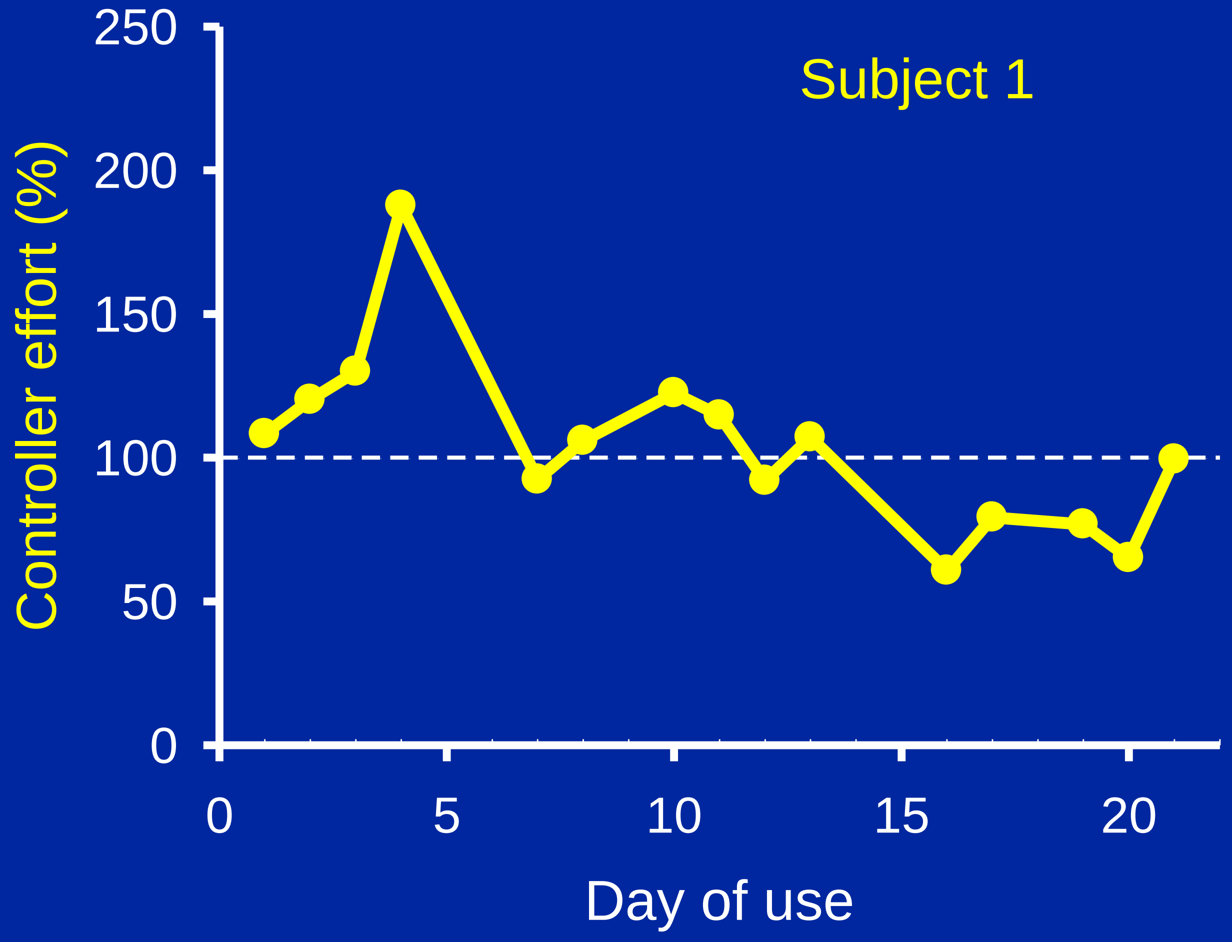
	Closed loop N = 16	Control N = 16
Number of severe hypoglycaemia	-	-
Number of elevated ketones during night or morning*	2	2
Number of subjects experiencing elevated ketones during night or morning*	2	1

* Plasma ketones > 1.5mmol/L

Utility analysis

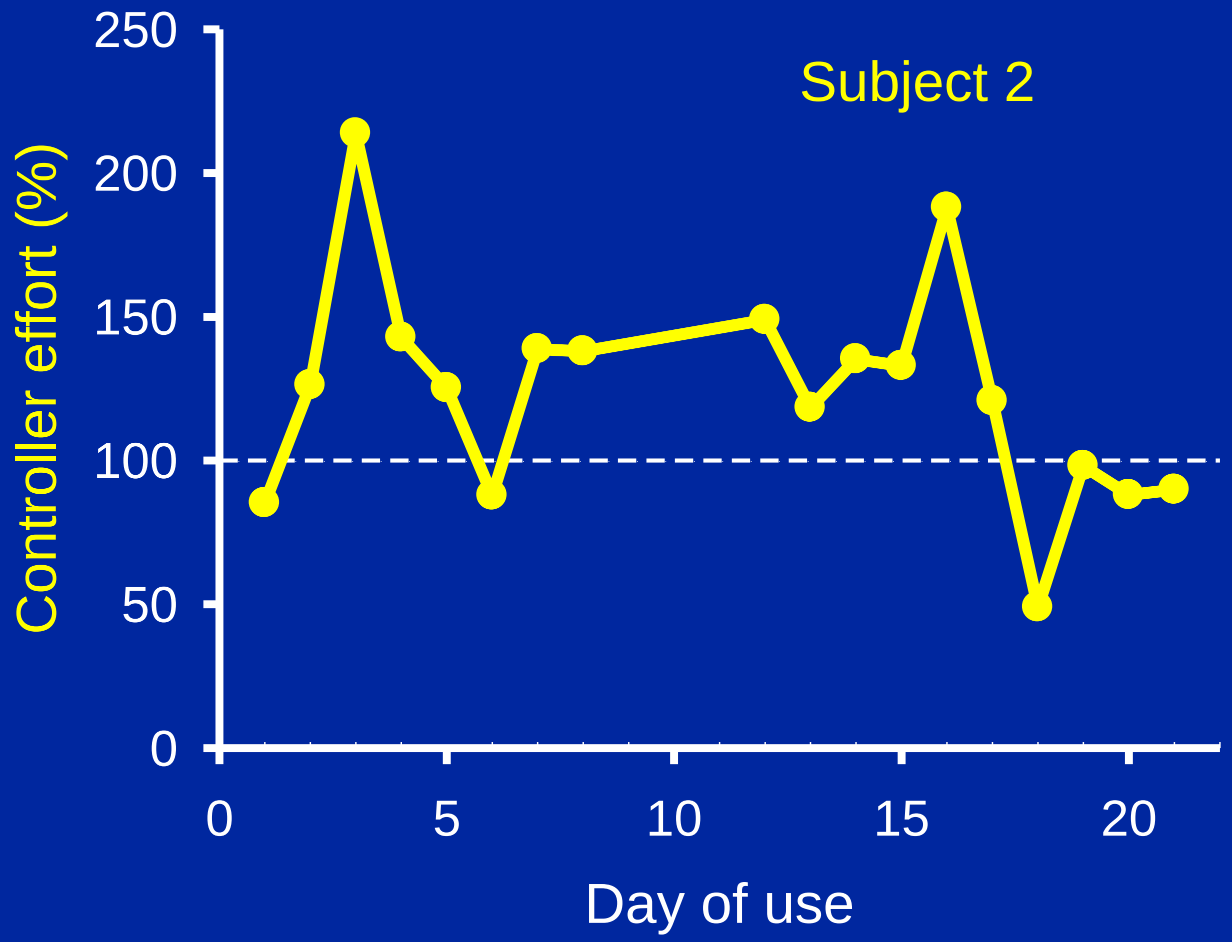
Number of nights when closed loop turned on	311 (93%)
Time of day when closed loop turned on	21:34 (20:37, 22:35)
Time of day when closed loop turned off	07:37 (07:01, 09:09)
Duration of closed loop operation (min)	601 (519, 696)

Controller effort 23:00 to 07:00

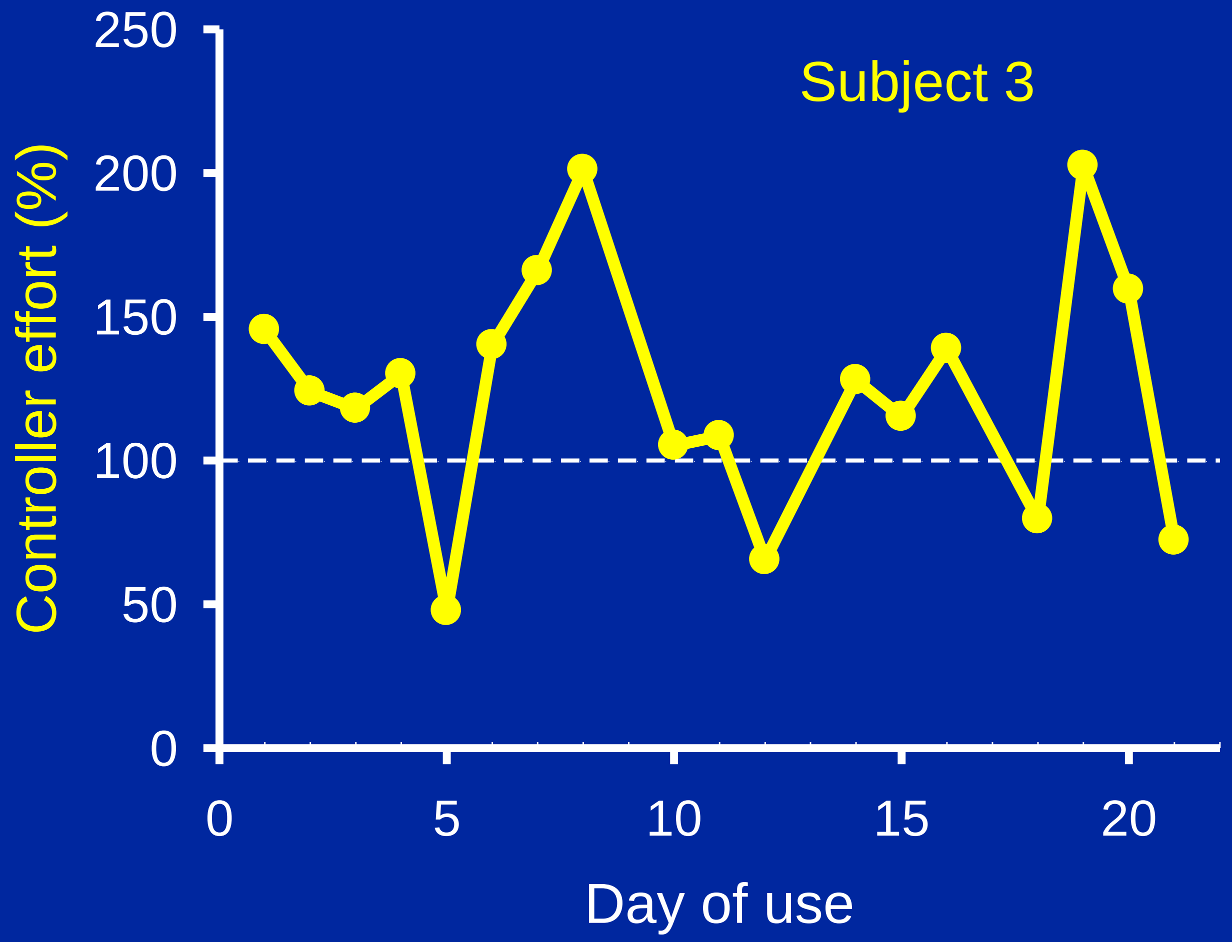


Controller effort - percentage of insulin relative to programmed basal

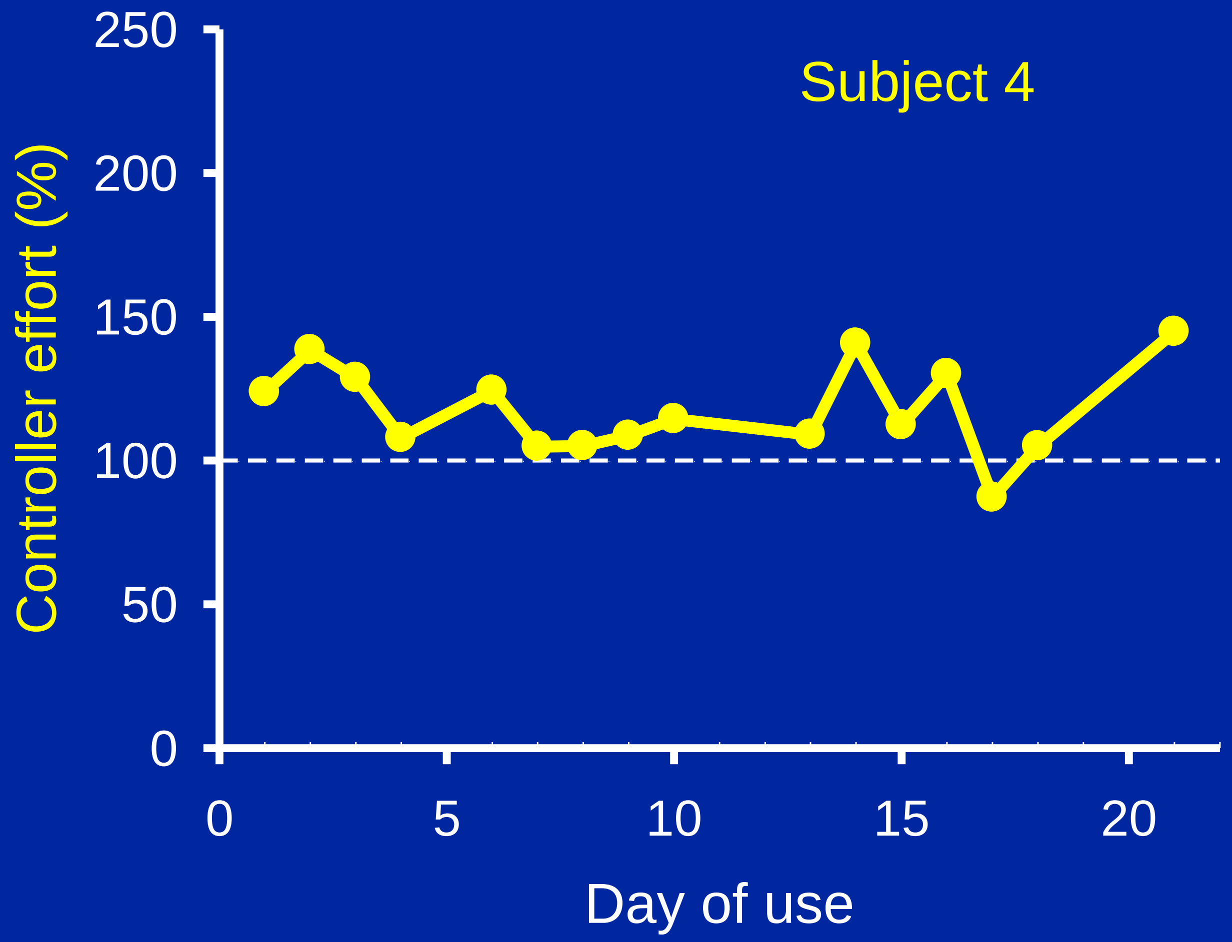
Controller effort 23:00 to 07:00



Controller effort 23:00 to 07:00



Controller effort 23:00 to 07:00



Key Positive Themes

- Reassurance
- Peace of mind
- Confidence
- Safety
- Improved diabetes control
- Sleep!
- ‘Not having to think about it’
- ‘Time off’ from diabetes demands
- Better control and feeling better during the first half of the day

Barnard *et al, BMJ Open Diab.Res.Care 2:* 2014

Key Negative Themes

- Calibration difficulties
- Size (of equipment and of sensors)
- Accuracy / trust
- Frustration when equipment ‘fails’
- Alarms (both positive and negative)
- Discomfort

Conclusions

- Unsupervised home use of overnight closed loop in adolescents with type 1 diabetes is
  - Safe
  - Feasible
- Glucose control improved during the night (and day) with fewer episodes of nocturnal hypoglycaemia

Other completed home studies

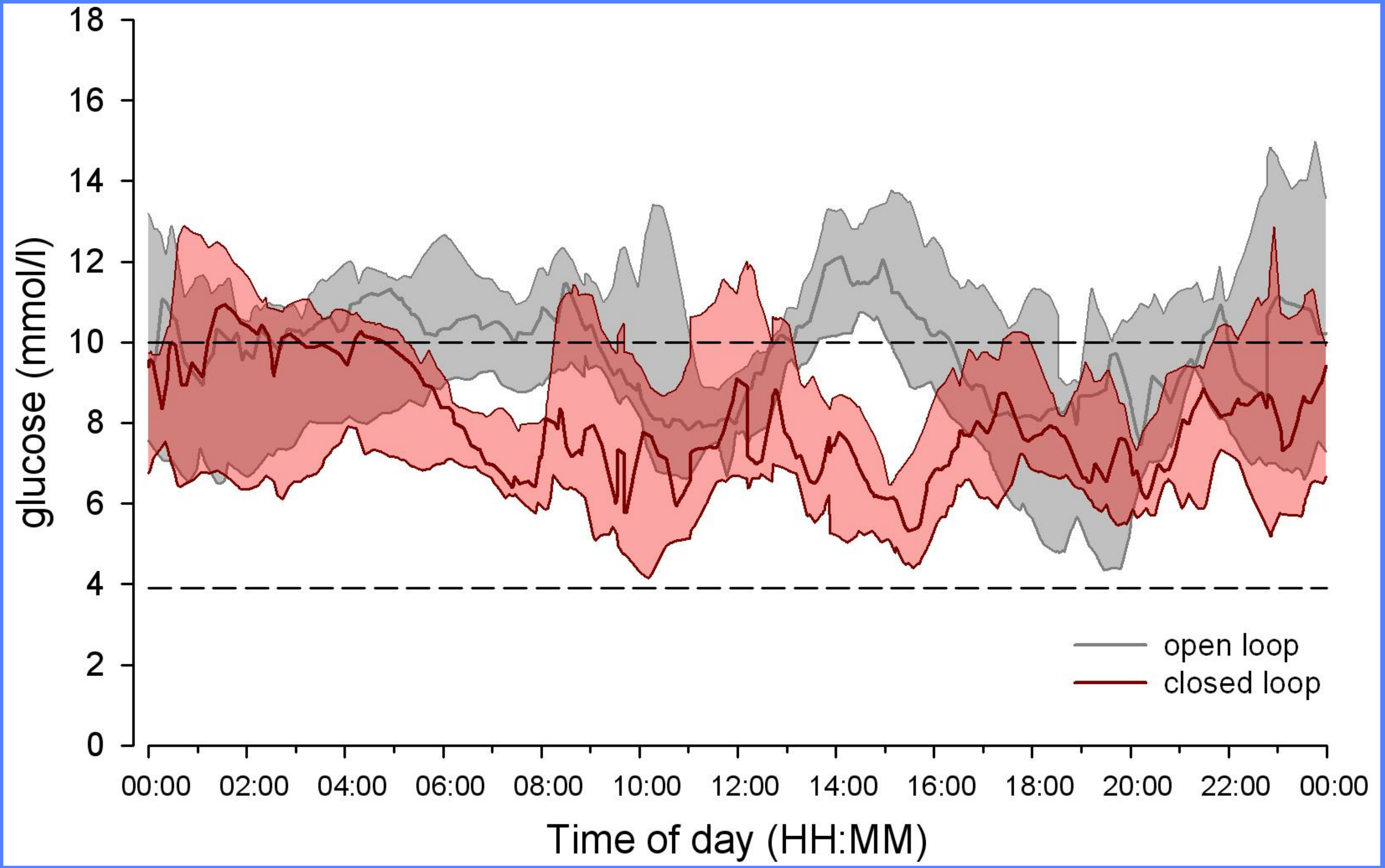
- Overnight multicentre closed loop in adults over four weeks
  - Cambridge
  - Kings College London
  - Sheffield

- Day-and-night multicentre multinational closed loop in adults over one week
  - Cambridge
  - Profil, Germany
  - Graz, Austria

Leelarathna *et al, Diabetes Care* 2014 (in press)

Florence during day-and-night use

Adult free living conditions over 7 days



Global effort

Artificial Pancreas clinical studies 2013/14

Threshold suspend

- R. M. Bergenstal *et al*. Threshold-based insulin-pump interruption. *N Engl J Med* 369 (3):224-232, 2013.
- T. T. Ly *et al .* Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. *JAMA* 310 (12):1240-1247, 2013.

Overnight

- M. Phillip *et al*. Nocturnal glucose control with an artificial pancreas at a diabetes camp. N.Engl.J.Med. 368 (9):824-833, 2013.
- R. Nimri *et al*. Night glucose control with MD-Logic artificial pancreas in home setting: a single blind, randomized crossover trial-interim analysis. *Pediatr.Diabetes*, 2013.
- I. Capel *et al*. Artificial pancreas using a personalized rule-based controller achieves overnight normoglycemia in patients with type 1 diabetes. *Diabetes Technol.Ther.* 16 (3):172-179, 2014.
- R. Hovorka *et al*. Overnight closed loop insulin delivery in young people with type 1 diabetes: A free-living randomised clinical trial. *Diabetes Care* 10.2337/DC13-2644, 2014.

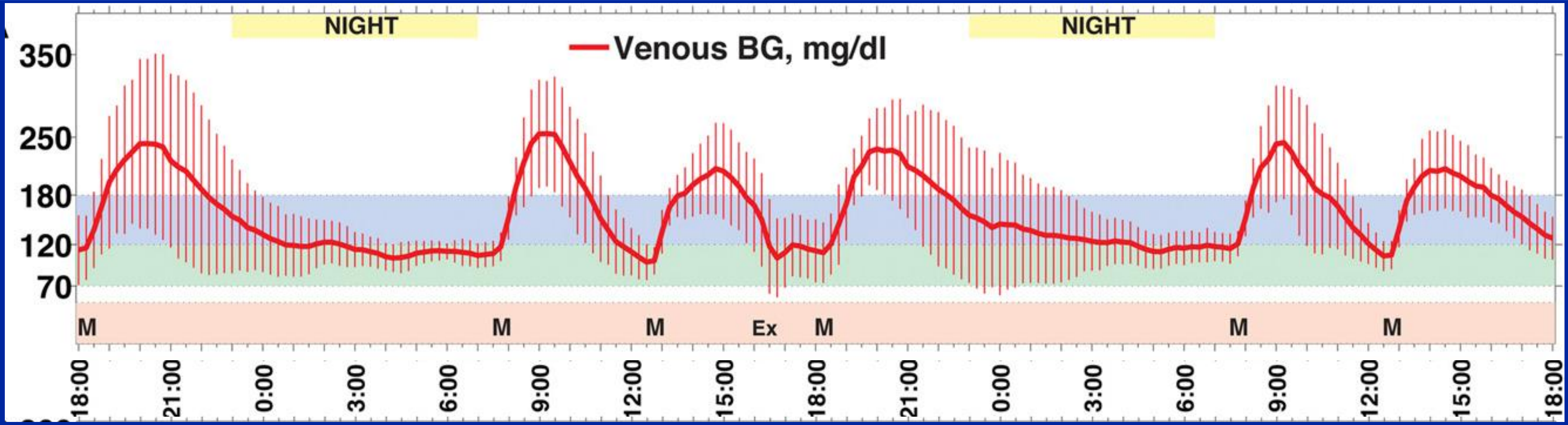
Day-and-night

- A. Dauber *et al*. Closed-loop insulin therapy improves glycemic control in children aged <7 years: a randomized controlled trial. *Diabetes Care* 36 (2):222-227, 2013.
- D. Elleri *et al*. Closed-loop basal insulin delivery over 36 hours in adolescents with type 1 diabetes: Randomized clinical trial. *Diabetes Care* 36 (4):838-844, 2013.
- E. Dassau, H. Zisser, R. A. Harvey, M. W. Percival, B. Grosman, W. Bevier, E. Atlas, S. Miller, R. Nimri, L. Jovanovic, and F. J. Doyle, III. Clinical Evaluation of a Personalized Artificial Pancreas. *Diabetes Care*, 2012.
- J. L. Sherr *et al*. Reduced hypoglycemia and increased time in target using closed-loop insulin delivery during nights with or without antecedent afternoon exercise in type 1 diabetes. *Diabetes Care* 10.2337/dc13-0010, 2013.
- B. P. Kovatchev *et al*. Feasibility of outpatient fully integrated closed-loop control: first studies of wearable artificial pancreas. *Diabetes Care* 36 (7):1851-1858, 2013.
- R. A. Harvey *et al*. Clinical Evaluation of an Automated Artificial Pancreas Using Zone-Model Predictive Control and Health Monitoring System. *Diabetes Technol.Ther.*, 2014.
- L. Leelarathna *et al*. Day and night home closed-loop insulin delivery in adults with type 1 diabetes: Three centre randomised crossover study. *Diabetes Care* 10.2337/DC13-2911, 2014.

Dual hormone (glucagon)

- A. Haidar *et al*. Glucose-responsive insulin and glucagon delivery (dual-hormone artificial pancreas) in adults with type 1 diabetes: a randomized crossover controlled trial. *CMAJ.* 185 (4):297-305, 2013.
- F. H. El-Khatib et al. Autonomous and continuous adaptation of a bihormonal bionic pancreas in adults and adolescents with type 1 diabetes. J Clin.Endocrinol.Metab:jc20134151, 2014.
- A. C. van Bon *et al*. Feasibility of a portable bihormonal closed-loop system to control glucose excursions at home under free-living conditions for 48 hours. *Diabetes Technol.Ther.* 16 (3):131-136, 2014.

Insulin and glucagon co-delivery

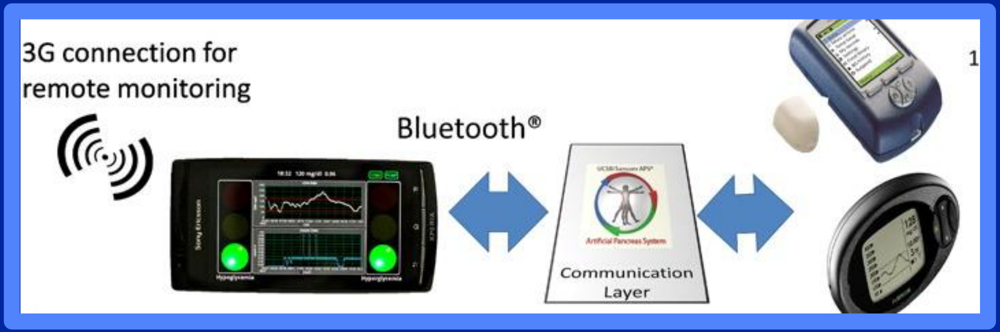


- N = 2x6 adults (48 hour study)
- Time in target 68% (3.9 – 8.0 mmol/l)
- Physiological glucagon levels
- 3 U meal priming bolus
- 8 hypoglycaemia events

Russell *et al*, Diabetes Care, 2012

Home/integrated prototypes (selection)

FlorenceD, Cambridge
(Navigator, Dana R Diabecare,
Ultramobile PC)



DiAS, iAP Group
(Dexcom Seven Plus, Insulet,
tablet, Android phone)

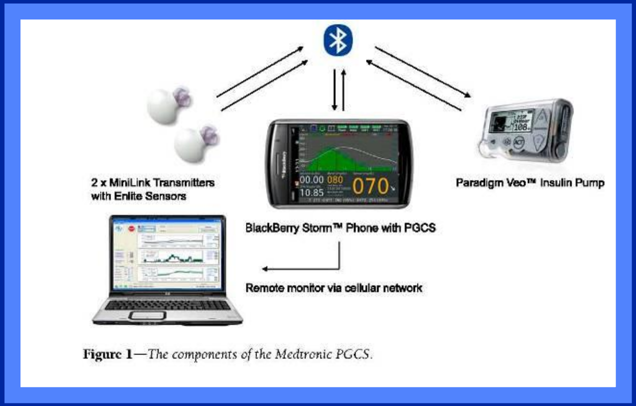


Figure 1—*The components of the Medtronic PGCS.*

PGCS, Medtronic
(Enlite, Veo,
Blackberry)

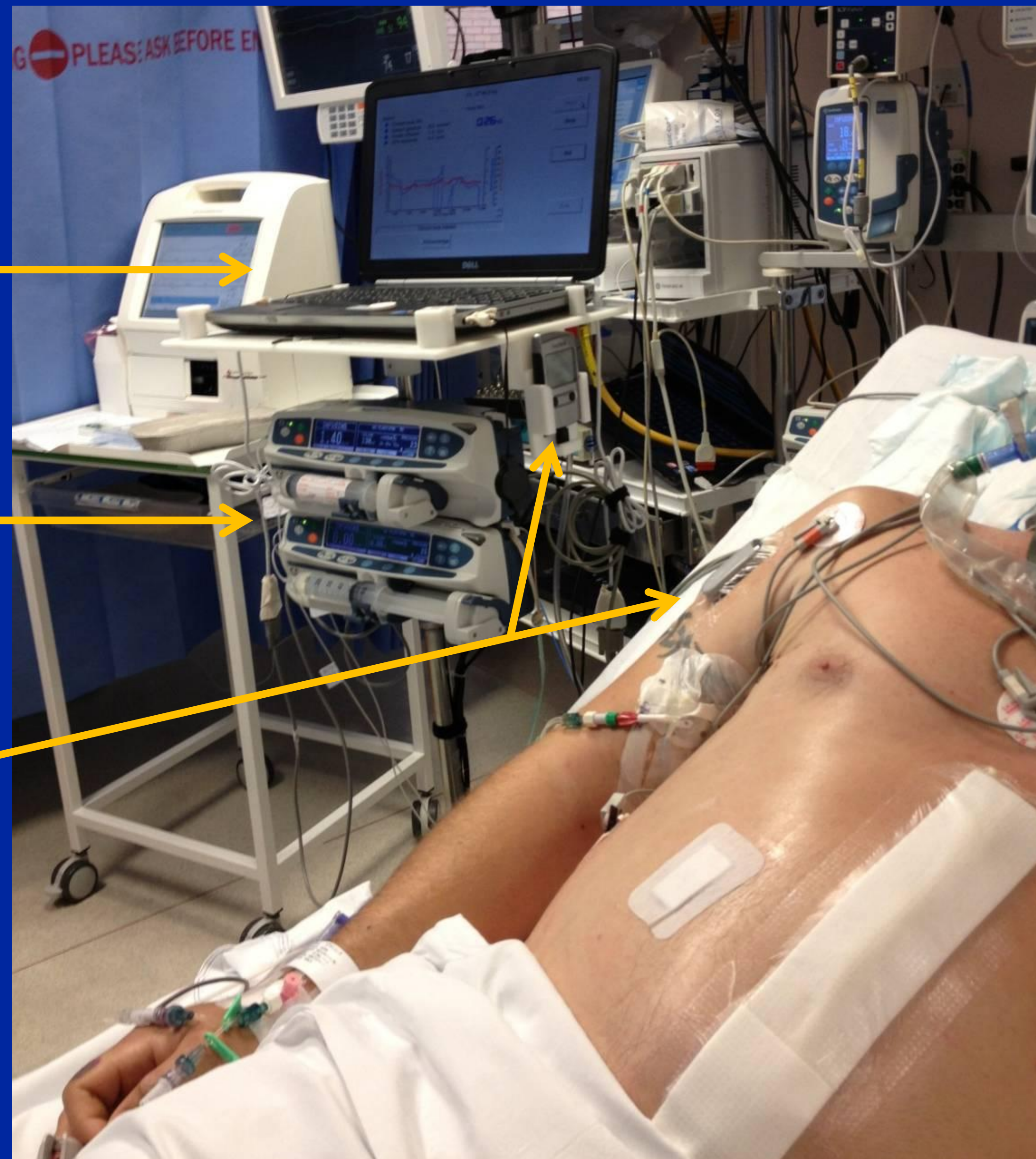
Elleri *et al*, Pediatr Diabetes, 13, 2012
Cobelli *et al*, Diabetes Care, 35, 2012
O’Grady *et al*, Diabetes Care, 2013

Closed-loop in critically ill

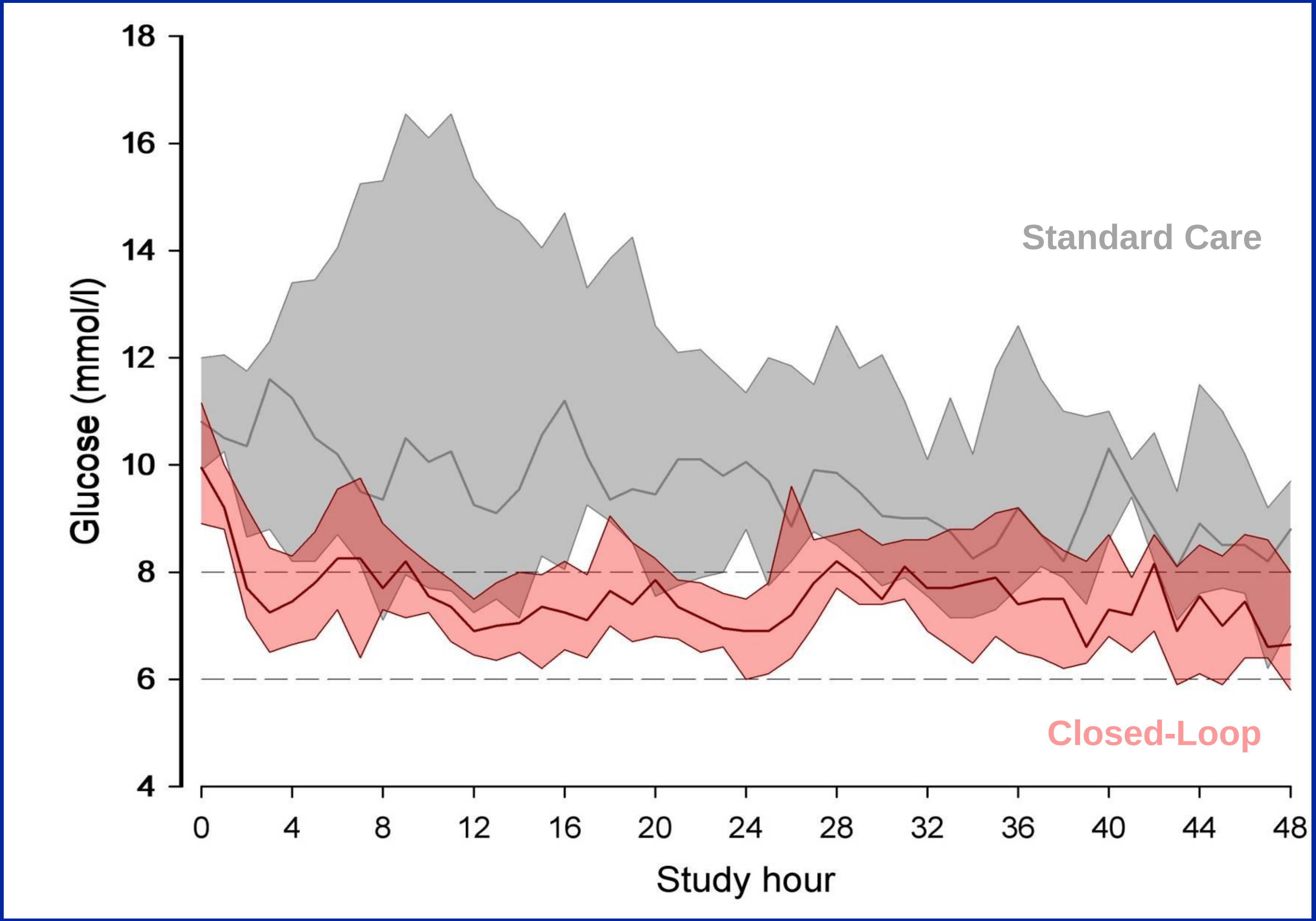
Computer running MPC algorithm

Insulin and Dextrose pumps

Glucose sensor & Navigator

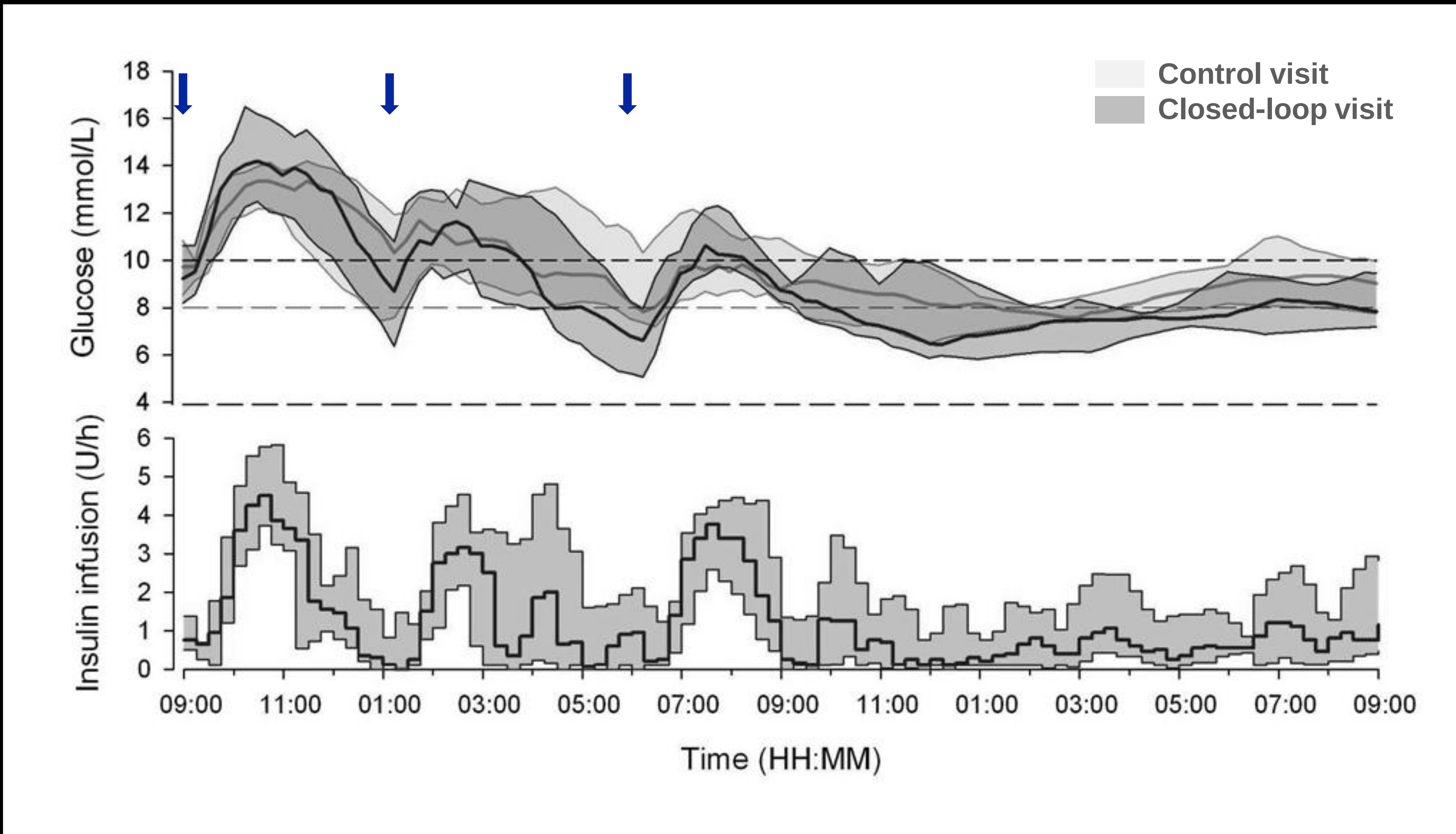


Glucose profiles (N = 2 x 12)



Leelarathna *et al, Crit Care 17:* 2013

Fully closed loop in type 2 diabetes



Kumareswaran *et al, Diabetes Care 37:* 2014

Early observations from home studies

- Unsupervised free living use
  - Over 8,000 hours
  - Over 1,000 nights
  - Over 100 day-and-nights
- Overnight and day-and-night closed-loop feasible
- Results suggest benefit from closed-loop

What next?

- Children and adolescents type 1 diabetes
  - 3 months multicentre overnight closed-loop
  - 7 days day-and-night closed-loop

- Adults type 1 diabetes
  - 3 months multicentre multinational overnight closed-loop day-and-night

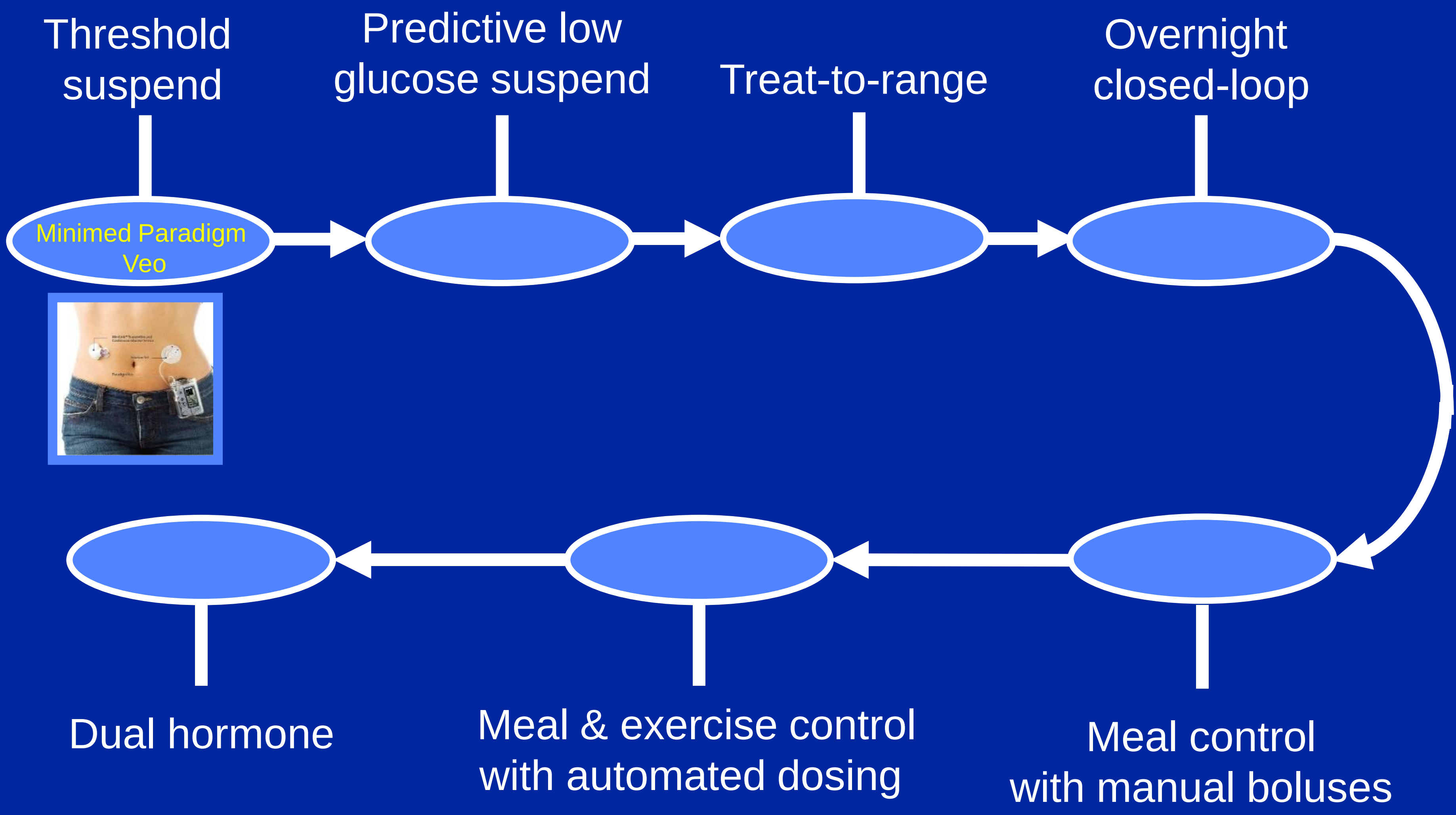
- Adults type 2 diabetes
  - 3 days day-and-night closed loop on the general ward

Next generation closed loop prototype

Largest challenges

- Sensor reliability
- Speed of insulin absorption
- Patient selection
- Instrumentation/integration
- What happens when closed loop stops running

Closed-loop generations



Cambridge colleagues – work of passion


David Dunger


Mark Evans


Helen Murphy


Rowan Burnstein


Anthony Coll


Carlo Acerini


Janet Allen


Ranna El Khairi


Daniela Elleri


Sam Goode


Arti Gulati


James Graveston


Ahmad Haidar


Julie Harris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Kavita Kumareswaran


Lalantha Leelarathna


Jasdip Mangat


Marianna Nodale


Hood Thabit


Gosia Wilinska

Martina Biagioni
Karen Caldwell
Ludovic Chassin
Allesandra De Palma
Giulio Maltoni
Angie Watts
Paul White

UK and further afield

- **King's College**
  - Stefanie Amiel
  - Pratik Choudhary
- **University of Sheffield**
  - Simon Heller
  - Emma Walkinshaw
  - Alexandra Solomon
- **University College London**
  - Peter Hindmarsh
- **Leeds Teaching Hospital**
  - Fiona Campbell
- **Norfolk and Norwich University Hospital**
  - Nandu Thalange
- **University of Surrey**
  - Margot Umpleby
  - Nicola Jackson
- **University of Southampton**
  - Kath Barnard
- **University of Swansea**
  - Steve Luzio
- **Triteq**
  - Steve Lane
- **Jaeb Centre**
  - John Lum
  - Craig Kollman
  - Peter Calhoun
  - Dongyuan Xing
- **University of Graz**
  - Thomas Pieber
  - Julia Mader
- **Profil Institute**
  - Lutz Heinemann
  - Carsten Benesch
  - Sabine Arnolds
- **University of Amsterdam**
  - J Hans DeVries
- **University of Padova**
  - Claudio Cobelli
  - Daniela
- **University of Montpelier**
  - Eric Renard
- **Pediatric Hospital of Luxembourg**
  - Carine de Beaufort

Participants and families










Funders and Support

JDRF
IMPROVING LIVES. CURING TYPE 1 DIABETES.

DIABETES UK
CARE. CONNECT. CAMPAIGN.

NHS
National Institute for Health Research

NIDDK
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

SEVENTH FRAMEWORK PROGRAMME

MRC
Medical Research Council

DRN
Diabetes Research Network

Abbott
Diabetes Care

smiths medical
bringing technology to life

Medtronic
Alleviating Pain · Restoring Health · Extending Life

Animas®
CORPORATION
a Johnson & Johnson company

dexcom™
THE GLUCOSE SENSOR COMPANY

Insulet Corporation

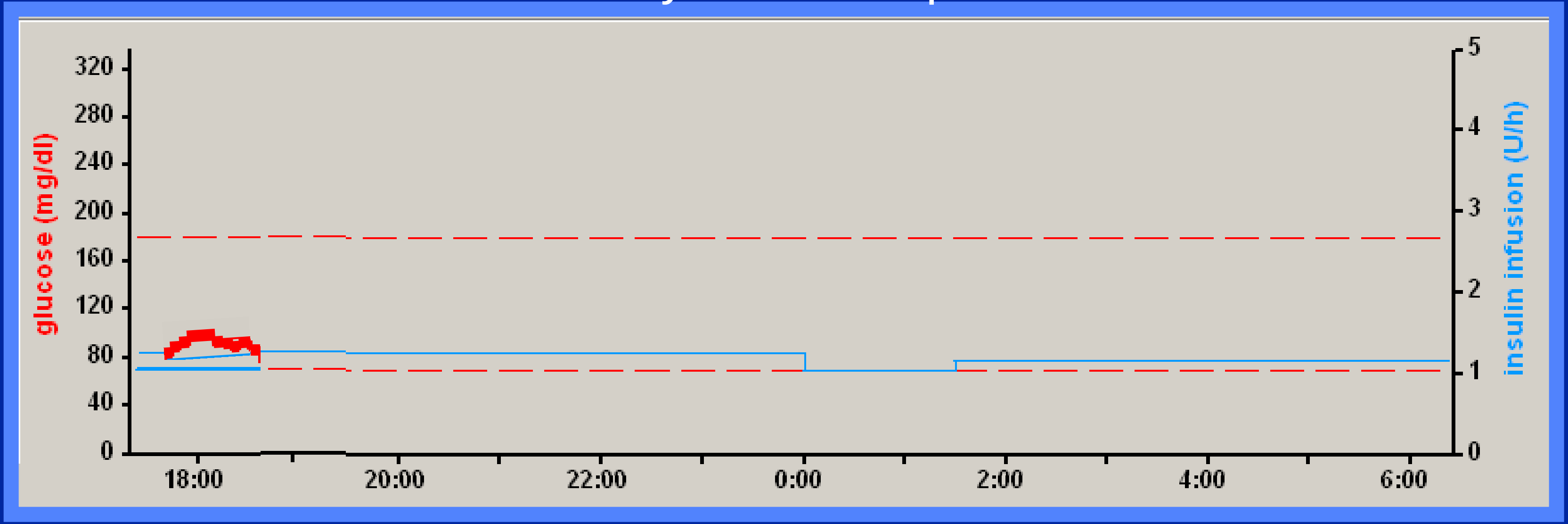
Edwards Lifesciences

Roche

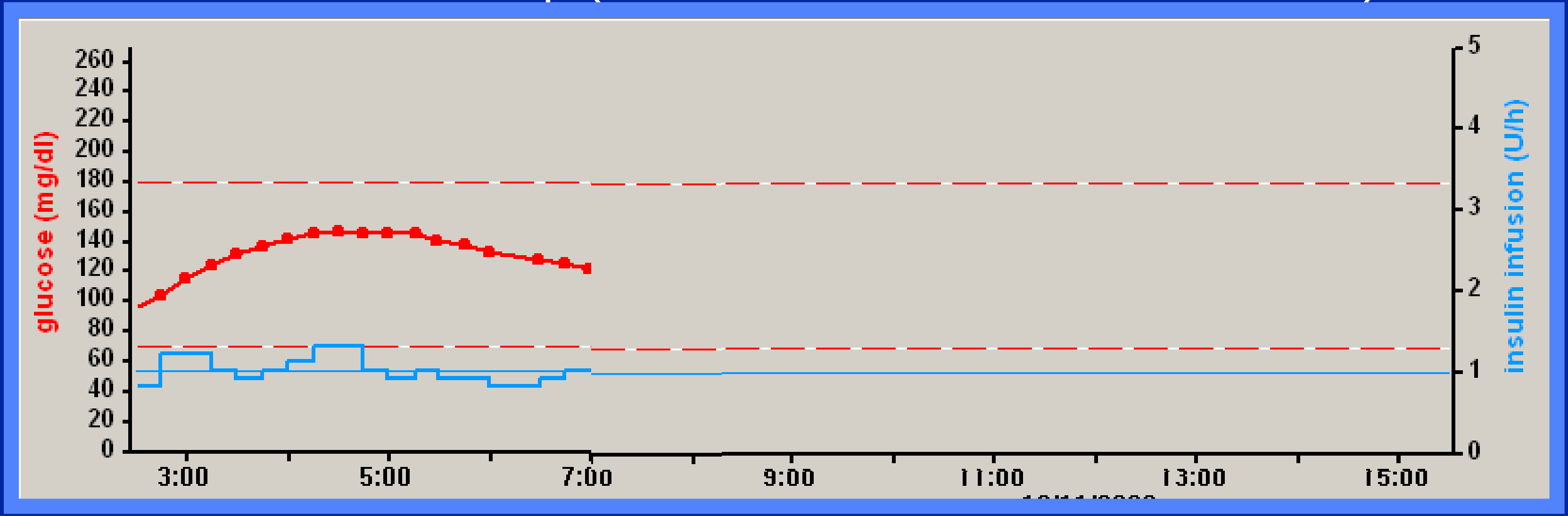
Thank you

Types of closed loop

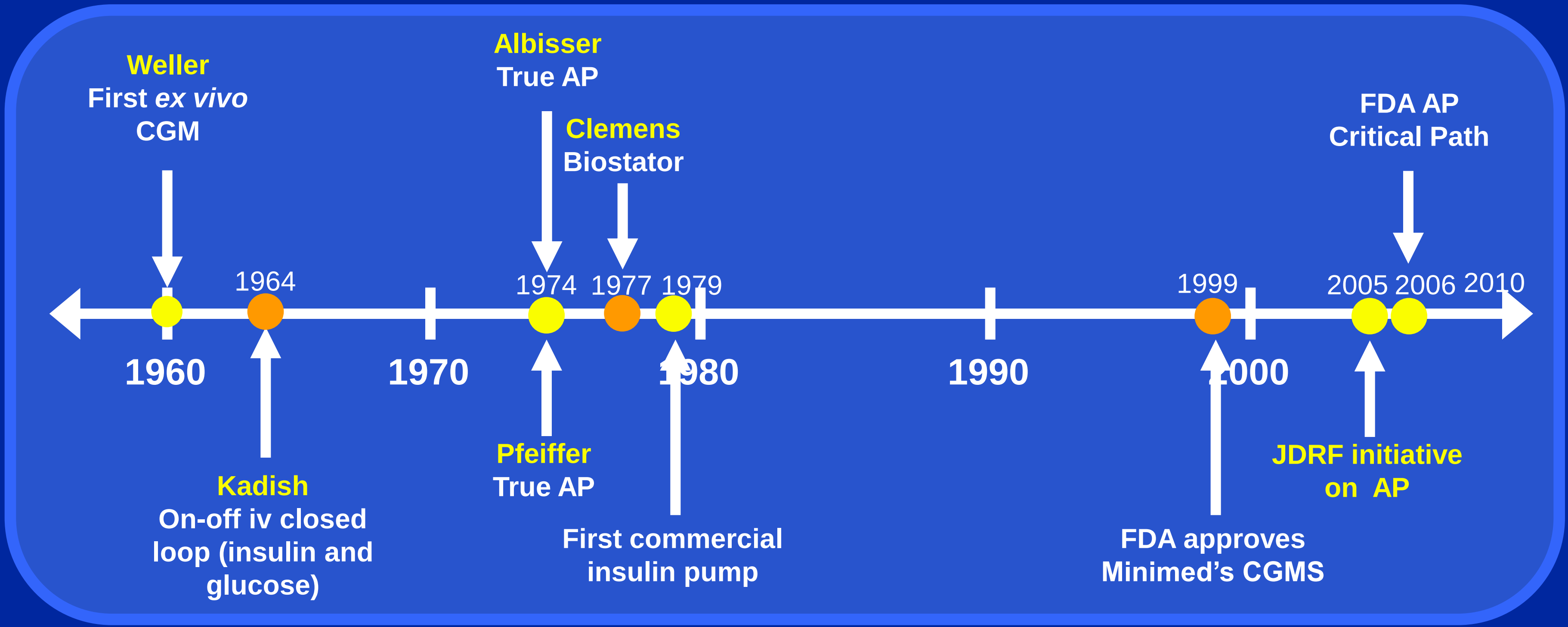
Fully closed loop



Semi-closed loop (meal announcement, feed forward)

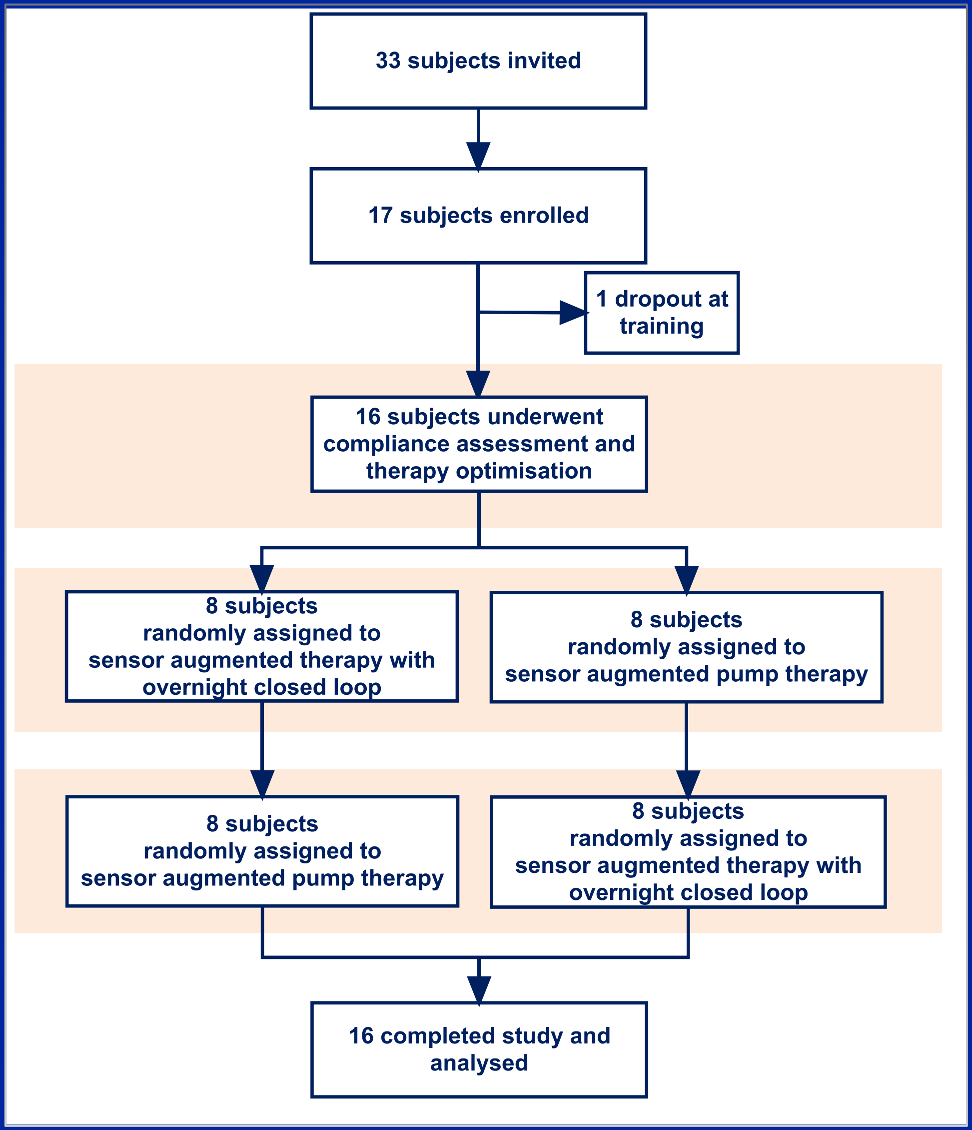


History


Weller
First *ex vivo* CGM
Albisser
True AP
Clemens
Biostator
FDA AP
Critical Path
1964
1974
1977
1979
1999
2005
2006
2010
1960
1970
1980
1990
2000
Kadish
On-off iv closed loop (insulin and glucose)
Pfeiffer
True AP
First commercial insulin pump
FDA approves Minimed's CGMS
JDRF initiative on AP


MiniMed
ACT
SEL

Flow of participants



Delays and blunting