Supplementary Appendix

Figure S1. Consort flow diagram

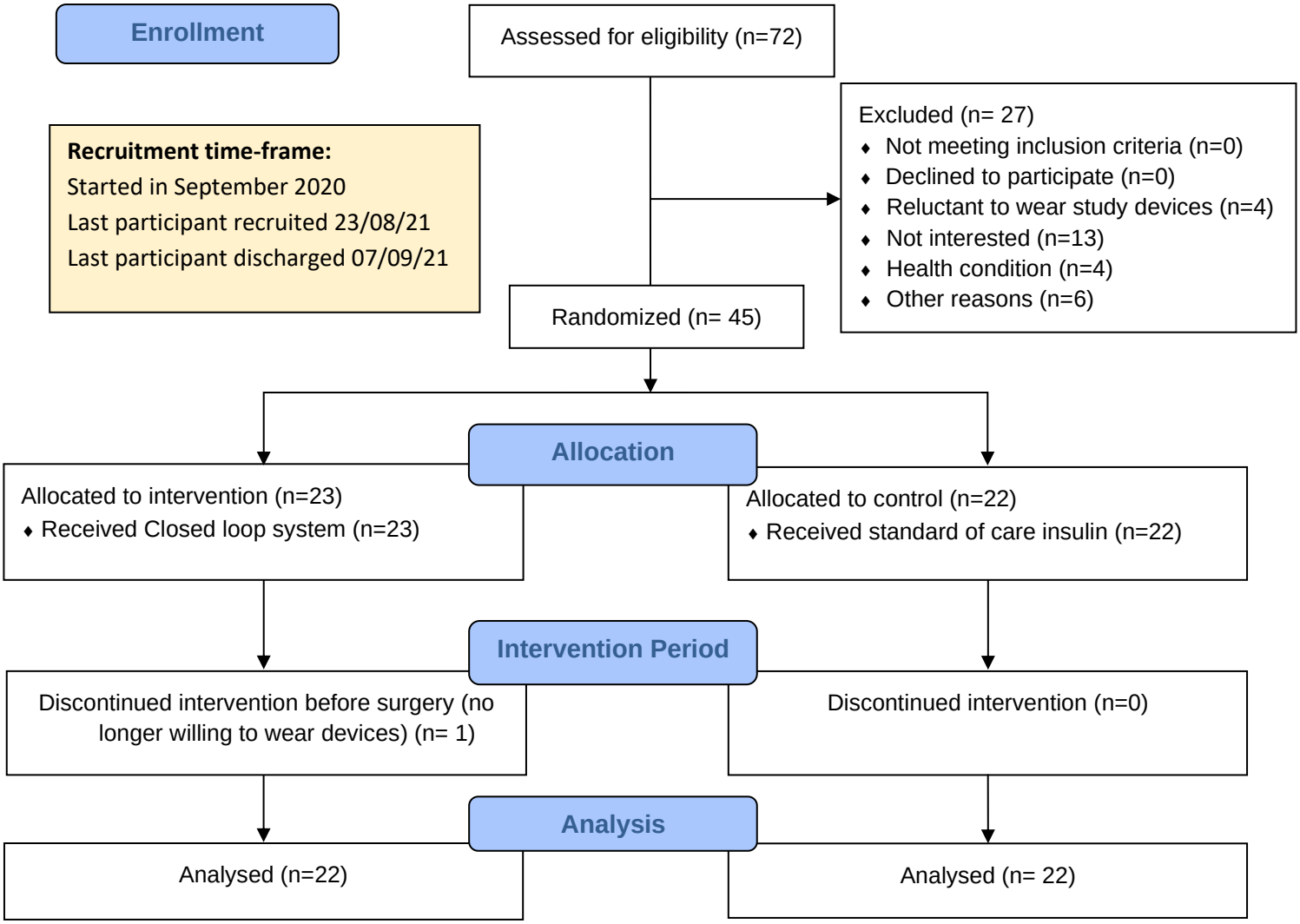

Figure S2. CamAPS HX fully automated closed-loop insulin delivery system.

Table S1. Eligibility criteria

Participants fulfilling all of the following inclusion criteria were eligible for the study:

- Written informed consent
- The subject is aged 18 years or over
- Diagnosis of type 2 diabetes (or other non-type 1 diabetes) using standard diagnostic criteria
- The subject is planned for an elective abdominal, thoracic, cardiovascular or other type of elective surgery at the University Hospital Bern expected to last ≥2 hours
- The subject requires treatment with subcutaneous insulin as part of the perioperative glucose management
- The subject is literate in German and/or French
- The subject is willing to wear study devices 24/7

The presence of any one of the following exclusion criteria led to exclusion of the participant:

- Physical or psychological condition likely to interfere with the normal conduct of the study and interpretation of the study results as judged by the investigator
- Known or suspected allergy to insulin
- Type 1 diabetes
- Pregnancy, planned pregnancy, or breast feeding
- Medically documented allergy towards the adhesive (glue) of plasters or unable tolerate tape adhesive in the area of sensor placement
- Lack of safe contraception for female participants of childbearing potential for the entire study duration (medically reliable method of contraception are considered oral, injectable, or implantable contraceptives, intrauterine contraceptive devices, or any other methods judged as sufficiently reliable by the investigator in individual cases).
- Serious skin diseases located at areas of the body, which potentially are to be used for placement of the glucose sensor
- Illicit drug abuse or prescription drug abuse
- Incapacity to give informed consent
- Droplet/airborne isolation precautions
- Participation in another clinical trial that interferes with the interpretation of the study results

Table S2. Glucose control during and after surgery

	Closed-loop	Control	Group Difference	95% CI	p value
Surgery					
Proportion of time with sensor glucose level					
between 5.6 and 10.0 mmol/L (%)	56.5±37.0	52.9±36.0	3.6	[-18.7; 25.8]	0.748
between 3.9 and 10.0 mmol/L (%)	73.5±33.0	60.8±36.3	12.7	[-8.4; 33.8]	0.231
>10.0 mmol/L (%)	24.7±34.0	38.7±36.8	-14.0	[-35.5; 7.6]	0.198
< 3.0 mmol/L (%)	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	0.0	[0.0; 0.0]	0.081
< 3.9 mmol/L (%)	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	0.0	[-0.0; 0.0]	0.083
< 5.6 mmol/L (%)	0.0 [0.0; 22.6]	0.0 [0.0; 0.0]	0.0	[-0.0; 2.6]	0.061
> 20.0 mmol/L (%)	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	0.0	[0.0; 0.0]	0.340
Mean sensor glucose levels (mmol/L)	8.5±2.9	9.7±2.7	-1.2	[-2.9; 0.5]	0.158
SD sensor glucose levels (mmol/L)	1.4±1.0	1.2±0.7	0.2	[-0.4; 0.7]	0.514
CV sensor glucose levels (%)	17.0±12.3	12.8±7.3	4.2	[-2.0; 10.4]	0.181
Post-Surgery					
Proportion of time with sensor glucose level					
between 5.6 and 10.0 mmol/L (%)	77.4±11.5	54.2±21.1	23.2	[12.7; 33.6]	<0.001
between 3.9 and 10.0 mmol/L (%)	84.7±9.4	64.0±26.7	20.7	[8.3; 33.1]	0.001
>10.0 mmol/L (%)	15.0±9.2	34.4±27.6	-19.4	[-32.2; -6.6]	0.004
< 3.0 mmol/L (%)	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	0.0	[-0.0; 0.0]	0.204
< 3.9 mmol/L (%)	0.0 [0.0; 0.2]	0.0 [0.0; 0.6]	0.0	[-0.1; 0.04]	0.852
< 5.6 mmol/L (%)	5.9 [2.9; 8.5]	7.5 [1.0; 14.5]	-0.1	[-6.5; 3.3]	0.953
> 20.0 mmol/L (%)	0.0 [0.0; 0.0]	0.0 [0.0; 0.3]	0.0	[-0.0; 0.0]	0.005
Mean sensor glucose levels (mmol/L)	8.0±0.7	9.4±2.6	-1.4	[-2.6; -0.2]	0.021
SD sensor glucose levels (mmol/L)	2.0±0.4	2.5±0.8	0.5	[-1.0; -0.2]	0.006
CV sensor glucose levels (%)	24.5±4.1	27.6±7.1	-3.1	[-6.6; 0.5]	0.089

Data are mean±SD or median [25th; 75th percentile]. P values were computed using Welch T-test or Wilcoxon rank sum test. 95% CI is the 95% confidence interval for the difference in the location parameters (Difference in means or Hodges-Lehman estimator).

CV, Coefficient of variation; SD, Standard deviation

Table S3. Overnight (00:00-06:00) and daytime (06:00-00:00) glucose outcomes.

	Closed-loop	Control	Group Difference	95% CI	p-value
Day (06:00-00:00)					
Proportion of time with sensor glucose level					
between 5.6 and 10.0 mmol/L (%)	74.4±11.1	52.9±23.6	21.5	[10.1; 32.8]	<0.001
>10.0 mmol/L (%)	18.3±10.2	38.7±28.3	-20.5	[-33.6; -7.3]	0.003
< 3.0 mmol/L (%)	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	0.0	[0.0; 0.0]	0.643
< 3.9 mmol/L (%)	0.3 [0.0; 0.5]	0.0 [0.0; 0.2]	0.0	[0.0; 0.4]	0.098
< 5.6 mmol/L (%)	5.1 [3.9; 8.3]	2.5 [1.2; 9.3]	1.7	[-1.9; 4.0]	0.245
> 20.0 mmol/L (%)	0.0 [0.0; 0.0]	0.0 [0.0; 0.3]	0.0	[0.0; 0.0]	0.314
Mean sensor glucose levels (mmol/L)	8.2±0.8	9.8±2.6	-1.6	[-2.7; -0.4]	0.013
SD sensor glucose levels (mmol/L)	2.2±0.5	2.6±0.8	-0.4	[-0.8; -0.01]	0.043
CV sensor glucose levels (%)	26.7±4.2	27.2±7.1	0.5	[-4.1; 3.0]	0.747
Night (00:00-06:00)					
Proportion of time with sensor glucose level					
between 5.6 and 10.0 mmol/L (%)	81.3±12.0	59.9±23.1	21.4	[10.2; 32.8]	<0.001
>10.0 mmol/L (%)	10.2±10.1	20.9±25.0	-10.7	[-22.5; 1.1]	0.074
< 3.0 mmol/L (%)	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	0.0	[0.0; 0.0]	0.301
< 3.9 mmol/L (%)	0.0 [0.0; 0.2]	0.0 [0.0; 0.4]	0.0	[-0.1; 0.0]	0.324
< 5.6 mmol/L (%)	4.4 [2.3; 12.6]	9.8 [1.4; 32.8]	-5.0	[-17.1; 1.8]	0.217
> 20.0 mmol/L (%)	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	0.0	[0.0; 0.0]	0.166
Mean sensor glucose levels (mmol/L)	7.6±0.9	8.3±2.0	-0.7	[-1.8; 0.5]	0.266
SD sensor glucose levels (mmol/L)	1.7±0.5	2.1±1.1	-0.4	[-1.0; 0.1]	0.090
CV sensor glucose levels (%)	21.4±5.8	25.1±9.5	-3.7	[-8.5; 1.1]	0.122

Data are mean±SD or median [25th; 75th percentile]. P-values were computed using Welch T-test or Wilcoxon rank sum test. 95% CI is the 95% confidence interval for the difference in the location parameters (Difference in means or Hodges-Lehman estimator).
CV, Coefficient of variation; SD, Standard deviation

Table S4. Postoperative characteristics

	Closed-loop	Control
Number of participants receiving IV insulin	3 (13.6%)*	8 (36.4%)
Number of participants receiving glucocorticoids	3 (13.6%)	3 (13.6%)
Number of participants requiring nutrition support		
Parenteral nutrition	7 (31.8%)	7 (31.8%)
Enteral nutrition	3 (13.6%)	4 (18.2%)
Number of participants with a post-operative IMC stay	9 (40.9%)	8 (36.4%)
Number of participants with a transient ICU stay	2 (9.1%)	0 (0%)
Length of stay (days)	9.5 [5.0; 15.3]	9.4 [4.8; 13.0]
Clavien-Dindo index (number of participants)		
Grade I	8 (36.4%)	10 (45.5%)
Grade II	8 (36.4%)	8 (36.4%)
Grade III	5 (22.7%)	3 (45.4%)
Grade IV	1 (4.5%)	1 (13.6%)

Data are median [25th; 75th percentile] or n (%). IV, Intravenous; ICU, Intensive Care Unit; IMC, Intermediate Care Unit.
*During study suspension (the number of hours spend in the ICU were 15 and 19 hours, respectively).

Table S5. Surgery characteristics

	Closed-loop	Control
Number of participants receiving a pre-surgery carboloading	8 (36.4%)	1 (4.5%)
Surgery duration (min)	256.6 (128.9)	267.0 (111.4)
Number of participants receiving IV insulin	3* (13.6%)	13 (59.1%)
Number of participants receiving glucocorticoids	14 (63.6%)	16 (72.7%)

Data are mean [SD] or n (%). *for hyperkalemia correction

Table S6. List of surgeries

Closed-loop group	Control group
Laparoscopic hemi-colectomy (1)	Cerebral vascular surgery (1)
Laparoscopic liver resection (1)	Diagnostic laparoscopy, peritoneal biopsies (1)
Laparoscopic pancreatic head resection (2)	Laparoscopic liver resection (1)
Laparoscopic sleeve gastrectomy (1)	Laparoscopic pancreatic head resection (3)
Major vascular surgery (5)	Liver resection (1)
Open liver resection (1)	Major vascular surgery (5)
Open lung surgery (1)	Neurosurgery (1)
Open total pancreatectomy (2)	Open hernia repair (1)
Open pancreatic head resection (2)	Open Lung surgery (1)
Osteosynthesis lower limb (1)	Open pancreatic head resection (1)
Right trigeminal decompression (1)	Open total pancreatectomy (2)
Spine surgery (2)	Partial liver resection (1)
Small bowel adhesiolysis, peritoneal biopsies (1)	Rectal resection (1)
Total thyroidectomy (1)	Spine surgery (2)

(n) is the number of patients undergoing the respective surgery

Perioperative closed-loop insulin delivery versus standard insulin therapy – a randomised controlled parallel clinical trial in adults with type 2 diabetes (POP-LOOP)

Short-running title: Perioperative closed-loop glucose control **(POP-LOOP)**

Study Type:	Clinical trial with a CE-marked Medical Device (CE 698580)
Study Categorisation:	Risk category A according to HRA
Study Registration:	Clinicaltrials.gov NCT04361799
Study Identifier:	POP-LOOP
Sponsor-Investigator:	Dr Lia Bally, MD PhD Department of Diabetes, Endocrinology, Nutritional Medicine, and Metabolism Inselspital Bern, Bern University Hospital and University of Bern Freiburgstrasse 15 3010 Bern, Switzerland Email: lia.bally@insel.ch
Investigational Product:	CamAPS HX (CE 698580)
Protocol Version and Date:	5.0, February 15, 2021

This protocol has been written in accordance with current ISO 14155:2011 standards

CONFIDENTIAL

Signature Page(s)

Study number	Clinicaltrials.gov NCT04361799
Study Title	Perioperative closed-loop insulin delivery versus standard insulin therapy – a randomised controlled parallel clinical trial in adults with type 2 diabetes (POP-LOOP)

The Sponsor-Investigator and trial statistician have approved the protocol version [5.0 (dated 15.02.2021)], and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ISO 14155 norm and the local legally applicable requirements.

Sponsor-Investigator:

Prof. Dr. Lia Bally

Bern, Feb 15, 2021

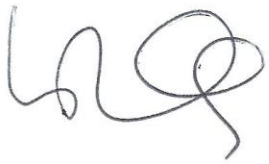

Table of Contents

STUDY SYNOPSIS

Sponsor-Investigator	Lia Bally MD PhD Department of Diabetes, Endocrinology, Nutritional Medicine, and Metabolism Inselspital Bern, Bern University Hospital and University of Bern Freiburgstrasse 15 3010 Bern, Switzerland
Study Title:	Perioperative closed-loop insulin delivery vs. standard insulin therapy – randomised controlled parallel clinical trial
Short Title / Study ID:	POP-LOOP
Protocol Version and Date:	Version 5.0 (dated 15.02.2021)
Trial registration:	ClinicalTrials.gov NCT04361799
Study category and Rationale	Category A according to HRO due to minimal risks and burdens of a CE-marked medical device
Clinical Phase:	Post-certification
Background and Rationale:	The prevalence of diabetes and hyperglycaemia in surgical patients is rising and associated with grater complication rates, length of stay and mortality rates. Suboptimal glucose management in the perioperative setting remains a major barrier to optimal surgical care. While there are guidelines to manage perioperative diabetes care, implementation is challenging and inconsistent, in part due to a stretched workforce, involvement of several disciplines and clinical teams and shortcomings in clinical training and knowledge. Closed-loop glucose control represents an emerging diabetes treatment modality that autonomously adjusts insulin delivery according to continuously measured glucose levels. The use of fully automated closed-loop insulin delivery may represent an easy-to-adopt approach for safe and effective perioperative diabetes management.
Objective(s):	The study objective is to compare fully automated closed-loop insulin delivery with standard insulin therapy in adults with type 2 diabetes undergoing elective surgery. 1. EFFICACY: The objective is to assess the ability of fully-automated closed-loop insulin delivery in maintaining sensor glucose levels within the target range from 5.6 to 10.0 mmol/L as compared to usual care in adults with type 2 diabetes undergoing elective surgery. 2. SAFETY: The objective is to evaluate the safety of fully automated closed-loop insulin delivery in terms of severe hypoglycaemic events (plasma glucose <2.2 mmol/L) and clinically significant hyperglycaemia (plasma glucose >20.0 mmol/L) with ketonaemia, and nature and severity of other device-related adverse events. 3. UTILITY: The objective is to determine the duration of use of the closed-loop system and the time spent for diabetes management as compared to usual care.

Outcome(s):	**Primary endpoint** The proportion of time spent in the target glucose range from 5.6 to 10.0 mmol/L based on CGM glucose levels during the time from hospital admission for elective surgery until discharge. **Secondary endpoints:** - Proportion of time spent with sensor glucose values above target (> 10.0 mmol/L) - Proportion of time spent with sensor glucose <3.0 mmol/L - Average of sensor glucose level - Time spent with sensor glucose below target (5.6 mmol/L) - Proportion of time spent with sensor glucose levels in significant hyperglycaemia (glucose levels > 20 mmol/L) - Standard deviation and coefficient of variation of sensor glucose levels - Total daily insulin requirements **Safety evaluation** Assessment of severe hypoglycaemic episodes (plasma glucose <2.2 mmol/L), clinically significant hyperglycaemia (>20.0 mmol/L) with ketonaemia (beta-hydroxybutyrate >1.0 mmol/L) and nature and severity of other adverse events that are related to the study procedures. **Utility evaluation** Assessment of the duration of use of the closed-loop system and time spent on diabetes management.
Study design:	Open label; randomised, parallel design, active control, clinical trial

Inclusion / Exclusion criteria:	**Key inclusion criteria:** 1. Written informed consent 2. Age 18 years or over 3. Diagnosis of type 2 diabetes using standard diagnostic practice (except for the accuracy study) 4. The subject is planned for an elective abdominal, thoracic, cardiovascular or other type of elective surgery at the University Hospital Bern expected to last ≥2 hours (cardiovascular surgery with the use of ECC for the accuracy study) 5. Deemed by clinical team to require insulin therapy for inpatient glycaemic control (except for the accuracy study) 6. Willingness to wear study devices 7. Literate in German and/or French **Key exclusion criteria:** 1. Physical or psychological condition likely to interfere with the normal conduct of the study and interpretation of the study results as judged by the investigator 2. Likely discharge earlier than 72 hours 3. Type 1 diabetes 4. Known or suspected allergy to insulin 5. Pregnancy or breast feeding 6. Medically documented allergic/irritative skin reactions to dressings/adhesives 7. Serious skin diseases located at places of the body, which potentially are possible to be used for localisation of the glucose sensor 8. Patients placed on droplet or airborne isolation precautions 9. Illicit or prescription drug abuse 10. Incapacity to give informed consent
Measurements and procedures:	Eligible participants will be randomly assigned to either have their blood glucose levels controlled using a fully automated closed-loop control system or standard insulin therapy according to local practice. Randomisation will be performed using a minimization method to balance the groups in terms of total daily insulin dose, BMI, surgical discipline and glucose control. Recruitment will be performed by referring clinicians during the pre-surgical evaluation procedures. On the day of hospital admission, participants will be fitted with the subcutaneous study continuous glucose monitor shortly after hospital admission to record interstitial glucose values throughout the study. The closed-loop system will be initialised once sensor glucose levels are available. The study will not interfere with nor specify any nutritional intake or activity of the patient during the hospitalisation. All other inpatient activities will be decided by the treating clinicians, as part of their routine clinical care. The study will conclude with hospital discharge or after a maximum of 20 days. At the end of the study the patient will be transferred to standard therapy according to existing hospital guidelines. In a pre-study pilot testing, the accuracy of the Dexcom G6 continuous glucose sensor will be evaluated in 15 adults undergoing cardiac surgery with hypothermic extracorporeal circulation (ECC). Sensor readings will be compared against venous blood glucose measurements from time of anaesthesia induction until hospital discharge.

Study intervention:	CamAPS HX closed-loop system comprising - Dexcom G6 real-time subcutaneous continuous glucose monitor (Dexcom, Northridge, CA, USA) - DANA RS subcutaneous insulin pump (Diabecare, Sooil, Seoul, South Korea) - An Android smartphone hosting the CamAPS HX application with the Cambridge model predictive control algorithm and communicating wirelessly with the insulin pump - Cloud upload system to monitor CGM/insulin data Participants' blood glucose levels will be controlled using the closed-loop system from hospital admission until discharge (maximum 20 days). The system operation is initiated using the participants' weight and estimated total daily insulin dose. During closed-loop operation, insulin will be adjusted automatically by the closed-loop insulin delivery system every 10 to 12 minutes according to sensor glucose values.
Comparator:	The control intervention will be standard insulin therapy according to local clinical practice and clinical team in charge of patient care during the hospital stay. Interstitial glucose levels will be recorded using the study continuous glucose monitor in blinded mode until hospital discharge (maximum 20 days).
Number of Participants with Rationale:	Forty adults with at least 48 hours of data. Samples size was calculated based on previous inpatient studies investigating fully automated closed-loop insulin delivery in patients with type 2 diabetes. In a pre-study pilot-testing, the accuracy of the continuous glucose sensor will be evaluated in 15 patients undergoing cardiac surgery during hypothermic extracorporeal circulation (ECC). Sample size was determined based on requirements for the calculation of accuracy metrics.
Study Duration:	Estimated duration from participant in and last participant out will be 12 months.
Study Schedule:	September 2020: First-Participant-In (planned) June 2021: Last-Participant-Out (planned)

Investigator(s):	Lia Bally, MD PhD Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism Inselspital, Bern University Hospital, University of Bern Freiburgstrasse 3010 Bern +41 31 632 36 77 Lia.bally@insel.ch Andreas Vogt, MD Department of Anaesthesiology and Pain Medicine Inselspital, Bern University Hospital, University of Bern Freiburgstrasse 3010 Bern +41 31 63 2 42 17 Andreas.vogt@insel.ch Dominik Günsch, MD Department of Anaesthesiology and Pain Medicine Inselspital, Bern University Hospital, University of Bern Freiburgstrasse 3010 Bern +41 31 632 03 77 Dominik.guensch@insel.ch Dr Salome Weiss MD Department of Cardiovascular Surgery Inselspital, Bern University Hospital, University of Bern Freiburgstrasse 3010 Bern Salome.weiss@insel.ch Alexander Kadner MD Department of Cardiovascular Surgery Inselspital, Bern University Hospital, University of Bern Freiburgstrasse 3010 Bern +41 31 63 2 11 68 Alexander.kadner@insel.ch Kocher Gregor MD Department of General Thoracic Surgery Inselspital, Bern University Hospital, University of Bern Freiburgstrasse 3010 Bern Gregor.kocher@insel.ch +41 31 63 2 74 86 Beat Gloor, MD Department of Visceral Surgery and Medicine Inselspital, Bern University Hospital, University of Bern Freiburgstrasse 3010 Bern + 41 31 63 2 24 77 Beat.gloor@insel.ch
Study Centre(s):	Single-centre (Inselspital, Bern University Hospital and University of Bern)

Statistical Considerations:	The trial is designed to have a power of 80% to detect a clinically significant between-group difference in the primary outcome of 20 percentage points with the use of a two-sided t-test and an alpha level of 0.05. To reflect heterogeneity among the participants, a standard deviation of ±30% for the primary outcome was used for the power calculation. Analysis will be performed according to the intention-to-treat principle. Analysis will be performed from the first available sensor reading of each intervention period until day 20 or hospital discharge. Data from all randomised participants with or without protocol violation including dropouts and withdrawals will be included in the analysis. Statistical analyses will be based on general linear modelling methods.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ISO EN 14155 as well as all national legal and regulatory requirements.

ABBREVIATIONS

Provide a list of abbreviations used on the protocol - to be completed

AE	Adverse Event
BASEC	Business Administration System for Ethical Committees, (https://submissions.swissethics.ch/en/)
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CRF	Case Report Form
ClinO	Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin, in Italian: OSRUm)*
eCRF	Electronic Case Report Form
CTCAE	Common terminology criteria for adverse events
DSUR	Development safety update report
ECC	Extracorporeal circulation
GCP	Good Clinical Practice
IB	Investigator's Brochure
Ho	Null hypothesis
H1	Alternative hypothesis
HRA	Federal Act on Research involving Human Beings *(in German: HFG, in French: LRH, in Italian: LRUm)*
IMP	Investigational Medicinal Product
IIT	Investigator-initiated Trial
ISO	International Organisation for Standardisation
ITT	Intention to treat
MD	Medical Device
MedDO	Medical Device Ordinance *(in German: MepV, in French: ODim)*
PI	Principal Investigator
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File

1. STUDY ADMINISTRATIVE STRUCTURE

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Monika Stucki acts as the monitor of this trial and has no further role in the preparation, execution or analysis of this trial.

Data Safety Monitoring Committee

Since the medical device under investigation is CE-marked, no Data Safety Monitoring Committee is intended for this study.

Any other relevant Committee, Person, Organisation, Institution

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2. ETHICAL AND REGULATORY ASPECTS

Approval of Ethics Committee Bern will be obtained before the commencement of any study-related activities. Any additional requirements imposed by the authorities shall be implemented.

Study registration

The study is registered in the Clinical Trials Registry Platform of the National Institute of Health (NIH) – ClinicalTrials.gov (NCT04361799). In addition, the trial will be registered in the Swiss National Clinical Trials Portal (SNCTP).

Categorisation of study

Risk category A.

Competent Ethics Committee (CEC)

The decision of the Ethics Committee Bern concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. Any requirements imposed by the Ethics Committee Bern authorities shall be implemented.

The Sponsor-Investigator will ensure the compliance with the following applicable reporting duties to the Ethics Committee Bern (Clin):

- Completion of the study (Art 83, ClinO): 90 days
- Discontinuation or interruption of the clinical trial (Art 83, ClinO): 15 days
- Safety events and annual safety report as specified in section 10.5
- Substantial amendments (see section 2.10)
- Final study report: within one year after completion of the study

All device-related safety events will be notified in line with Art. 15 of the Medical Devices Ordinance of the Therapeutic Products Act) and involve the local centre of materiovigilance. In addition, the manufacturer will be directly notified, as specified in the trial agreement.

Competent Authorities (CA)

Not applicable.

Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, the European Regulation on medical devices 2017/745 and the ISO Norm 14155 and ISO 14971 and the Swiss Law and Swiss regulatory authority's requirements. Declaration of interest

The Sponsor-Investigator declares no conflicts of interests.

Declaration of interest

The Sponsor-Investigator declares no conflict of interest with the conduct of this trial.

Patient Information and Informed Consent

Participants will be informed about the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary, that withdrawal is possible at any time and will not affect his/her subsequent medical assistance and treatment and that there will be no reimbursement for the participation in study apart from travel expenses.

The participant will be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All participants will be provided with a participant information sheet describing the objective of the study, study design and procedures as well as potential risks and benefits with sufficient detail to make an informed decision about participation in the trial. Participants will be given sufficient time for reflection.

The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study-related procedure.

The participant will be asked to read and consider the informed consent document before signing and dating it, and will be offered a copy of the signed document. The consent form will be also signed and dated by the investigator (or his designee) at the same time as the participant signs, and it will be retained as part of the study records.

Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy in line with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study will be considered confidential and will not be disclosed to third parties. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorised representatives of the Sponsor (-Investigator) or Ethics Committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

Early termination of the study

The Sponsor-Investigator may terminate the study prematurely in the following circumstances:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention

Protocol amendments

Any amendments made to the protocol must be approved by the Sponsor-Investigator.

Substantial amendments are only implemented after approval of the Ethics Committee Bern and entail the following according to ClinO Art. 29:

- Changes affecting the participants' safety and health, or their rights and obligations
- Changes to the protocol, and in particular changes based on new scientific knowledge which concern the trial design, the method of investigation, the endpoints or the form of statistical analysis
- Change of trial site, or conducting the clinical trial at an additional site
- Change of sponsor, coordinating investigator or investigator responsible at a trial site

The final decision whether the amendment under consideration is substantial or not will be at the discretion of the Ethics Committee Bern and communicated to Sponsor-Investigator

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Sponsor-Investigator and Ethics Committee Bern. Such deviations shall be documented and reported to the Sponsor-Investigator and the Ethics Committee as soon as possible.

All non-substantial amendments are communicated to the Ethics Committee as part of the Annual Safety Report.

3. BACKGROUND AND RATIONALE

Background and Rationale

Diabetes is the most common metabolic disorder, affecting one in every 11 adult worldwide (*1*). The growing prevalence of diabetes has major implications for health services including surgical inpatient care. Because diabetes-related comorbidities increase the need for surgical and other operative procedures, diabetes and hyperglycaemia are commonly encountered in the perioperative setting. It is estimated that 20-40% of non-cardiac, 35% of vascular, and up to 80% of cardiac surgery patients experience perioperative hyperglycaemia (*2-4*). The extent of hyperglycaemia in the perioperative setting is determined by several factors such as the type of diabetes and pre-existing level of glucose control, nutritional status, surgical-induced stress and use of medication such as glucocorticoids (*5-7*). There is a substantial body of literature demonstrating a clear association between suboptimal perioperative glucose control and adverse clinical outcomes including higher mortality in surgical patients (*2, 4, 8-11*). In a randomised multicentre trial involving a total of 211 patients with type 2 diabetes undergoing general surgery, the group receiving basal-bolus subcutaneous insulin achieved significantly better glycaemic control than those receiving a sliding scale insulin regimen (mean 8.0 vs. 9.5mmol/L, $p<0.01$) and a significantly reduced post-surgery comorbidity composite score consisting of wound infection, pneumonia, bacteraemia, and respiratory and acute renal failure (*12*). Another randomised controlled trial (n=164 patients) tighter glycaemic control (target 6.0mmol/L) initialised during hospital resulted in a significantly reduced incidence of infection in patients undergoing liver transplantation (*13*). In cardiac surgical patients, a 30% increase in the rate of adverse postoperative events was observed for every 1.1mmol/L increase in intraoperative glucose level (*14*). In addition to increased exposure to hyperglycaemia, previous work has also suggested that increased perioperative glycaemic variability is detrimental for surgical outcomes (*15, 16*). Of note, it was recently suggested that perioperative glucose control (averaged over the first 3 postoperative days) may be more important than preoperative A1C in predicting 30-day postoperative mortality (*17*).

Although studies striving for improved glucose control through the use of intensive insulin therapy showed beneficial results (*12, 13*), tighter glucose control inevitably results in an increased risk of hypoglycaemia which is similarly associated with worse medical outcomes (*18, 19*). Guidelines for achieving good perioperative glucose control are available but lack sufficient detail (*20*). There is therefore currently an unmet need for an easy-to-adopt approach for safe and effective perioperative management of hyperglycaemia.

Closed-loop glucose control systems, also known as the artificial pancreas, which automatically deliver insulin in a glucose-responsive manner, could potentially address this need, whilst reducing staff workload. Closed-loop systems combine real-time continuous glucose monitoring (CGM) with a control algorithm that directs insulin delivery via an insulin pump. Evidence that closed-loop technology improves glycaemic control in patients with hyperglycaemia is increasing, but its application in the perioperative setting including the intra-operative period has not been evaluated to date.

The aim of the present study is to contrast the efficacy, safety and usability of fully automated closed-loop insulin delivery with standard insulin therapy in patients with type 2 diabetes undergoing elective surgery at a tertiary hospital.

Investigational Product (treatment, device) and Indication

The CamAPS HX fully-automated closed-loop system is a CE-marked medical device manufactured by CamDiab Ltd (Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK) and its intended purpose is glucose control in hospital. For more details see Section 8.

Preclinical Evidence

The MPC algorithm of the Cambridge closed-loop systems has been studied extensively using *in silico* testing utilising simulator environments (*21, 22*).

Clinical Evidence to Date

Between 2011 and 2012, the Cambridge fully automated closed-loop system has been shown to be safe and feasible in insulin-naive patients with type 2 diabetes in a controlled research facility setting (*23*).

Between 2015 and 2016, the Cambridge fully-automated closed-loop system was evaluated in non-critical care patients with type 2 diabetes hospitalised in the fully automated general wards (*24*). Forty participants were randomised to either automated fully closed-loop insulin delivery or usual insulin therapy for a 72h study period. The proportion of time spent in the target glucose range (5.6-10.0mmol/L) was 59.8% in the closed-loop group and 38.1% in the control group (P<0.001). No episodes of severe hypoglycaemia or hyperglycaemia with ketonaemia occurred in either group.

In a larger study performed between 2016 and 2017 at the University Hospital Bern (Switzerland) and Cambridge (UK), 136 adults with type 2 diabetes hospitalised on medical or surgical wards were treated with either closed-loop insulin delivery or conventional subcutaneous insulin therapy for up to 15 days or until hospital discharge (*25*). The proportion of time spent in the target glucose range (5.6-10.0mmol/L) was 65.8% in the closed-loop group and 41.5% in the control group (P<0.001). No episodes of severe hypoglycaemia or hyperglycaemia with ketonaemia occurred in either group. A sub-analysis showed that patients receiving haemodialysis may particularly benefit from closed-loop by achieving 37.6% more time in target glucose range than during usual care (*26*).

In 2018, the Cambridge fully automated closed-loop system (n=21) was compared with conventional insulin therapy (n=22) in surgical and medical non-critical care patients receiving enteral and/or parenteral nutrition support at the University Hospital Bern (Switzerland) and University Hospital Cambridge (UK) (*27*). The proportion of time spent in the target glucose range (5.6-10.0mmol/L) was 68.4% in the closed-loop group and 36.4% in the control group (P<0.001).

In 2018, the Cambridge efficacy of the Cambridge fully automated closed-loop system using faster-acting insulin aspart vs. standard insulin aspart was evaluated in outpatients with type 2 diabetes in a controlled research facility setting (*28*).

An ongoing two-centre randomised crossover study (University Hospital Bern and University Hospital Cambridge) contrasts the efficacy, safety and usability of a fully automated closed-loop insulin delivery contrasted with usual insulin therapy in adult outpatients receiving dialysis (NCT04025775).

A recently completed study assessing the performance of the Dexcom G6 CGM during complex elective abdominal surgery at the University Hospital Bern showed satisfactory accuracy (median ARD of 9.9%), supporting that it can be safely used in the perioperative setting (*29*).

Explanation for choice of comparator

The comparator is standard insulin therapy in accordance with local practice of perioperative diabetes care in the University Hospital Bern. Standard care may include subcutaneous and intravenous insulin administration as judged by the treating clinical team.

Risks / Benefits

A potential key benefit of closed-loop insulin delivery is a reduction of both hyperglycaemic and hypoglycaemic episodes which have been shown to be associated with adverse medical outcomes, including perioperative complications, longer hospital stay and increased mortality (*2*, *12*, *18*). Additionally, the use of continuous glucose monitoring and automation of insulin delivery through closed-loop systems may reduce staff workload and reduce the risk of errors (*30*). This is particularly impactful to improve patient safety given that 31% of inpatients with diabetes have a medication error during their hospital stay and there is a statistically significant increased risk of prescription errors if treated on a surgical ward compared with a medical ward (*31*, *32*).

Any potential risks presented by the use of closed-loop glucose control have been minimized by adequate testing and incorporation of safeguards in accordance with EN ISO 14971:2012 Medical Devices — Application of Risk Management to Medical Devices. To mitigate against any residual risks that are inherent to any form of insulin therapy, adequate safety monitoring through the use of automated alerts will be implemented during the conduct of this study.

The maximal total blood draw volume during the pilot-testing (sensor accuracy assessment) will be 24ml which is considered a negligible quantity.

Justification of choice of study population

The study population will consist of adults with insulin-treated type 2 diabetes undergoing elective abdominal, thoracic,cardiovascular or other type of elective surgery of ≥2 hours duration. This population requires a work-intensive perioperative glucose management involving different clinical teams and improvement of glucose control whilst avoiding hypoglycaemia has the potential to contribute to better post-operative outcomes. The selected surgical disciplines is related to the geographical proximity within the University Hospital Campus. No vulnerable people will be enrolled into this clinical trial.

4. STUDY OBJECTIVES

Overall Objective

The purpose of this study is to assess the efficacy, safety and usability of perioperative fully-automated closed-loop insulin delivery versus standard insulin therapy in patients with type 2 diabetes undergoing elective surgery.

Primary Objective

The objective is to assess the ability of fully-automated closed-loop insulin delivery in maintaining continuous glucose monitoring (CGM) glucose levels within the target range from 5.6 to 10.0 mmol/L as compared to standard insulin therapy in adults with type 2 diabetes undergoing elective surgery.

Secondary Objectives

Secondary objectives include the effect of fully closed-loop insulin delivery on other CGM-based outcomes, insulin requirements and time spent on diabetes management.

Safety Objectives

Safety objectives include the assessment of frequency and severity of clinically significant hypoglycaemic and hyperglycaemic episodes and nature and severity of other adverse events.

5. STUDY OUTCOMES

Primary Outcome

The primary outcome is the time spent in the target glucose range from 5.6 to 10.0mmol/L from hospital admission to hospital discharge or a maximum of 20 days based on continuous glucose monitoring (CGM). The target range was defined based on recommendations from international societies such as the American Diabetes Association (*33*) and Society for Ambulatory Anaesthesia (*34*).

Secondary Outcomes

Secondary outcomes are:

- Proportion of time spent with sensor glucose values above target (> 10.0 mmol/L)
- Proportion of time spent with sensor glucose values < 3.0 mmol/L
- Average sensor glucose level
- Proportion of time spent with sensor glucose below target (<5.6 mmol/L)
- Standard deviation and coefficient of variation of sensor glucose levels
- Total daily insulin dose (U/24h)
- Average time spent on diabetes management
    - from hospital admission to discharge from the post-anaesthesia care unit
    - daily in the intermediate care unit
    - daily on the general wards

Other Outcomes of Interest

Other outcomes of interest are:

- Characteristics of surgery (discipline, procedure, duration as defined from skin incision to closure, type of anaesthesia)
- Proportion of time when closed-loop was active
- Post-surgery comorbidity as assessed using the Clavien Dindo Classification (*35*) by the surgical team
- Length of Hospital stay
- Modality of insulin treatment in the control group (intravenous vs. subcutaneous)
- Use of glucocorticoids (intra- vs. post-operative vs. both)
- Use of parenteral/enteral nutrition support
- Stay in the intensive care unit (planned vs. unplanned)
- Accuracy of the Dexcom G6 continuous glucose sensor during hypothermic extracorporeal circulation (ECC)

Safety Outcomes

Safety outcomes will include severe hypoglycaemia (<2.2 mmol/L) and clinically significant hyperglycaemia (>20.0 mmol/L) with ketonaemia (beta-hydroxybutyrate >1.0 mmol/L), as determined by point-of-care capillary measurements, as well as other (serious) adverse events related to the study procedures (*36*).

6. STUDY DESIGN

General study design and justification of design

The clinical trial will adopt a randomised, open-label, single-centre two-group, parallel design. We plan to recruit 40 adults with insulin-treated type 2 diabetes undergoing elective abdominal, thoracic, cardiovascular or other type of elective surgery at the University Hospital Bern. Eligible participants will be randomly assigned (1:1) to either fully automated closed-loop insulin delivery (closed-loop group) or local standard insulin therapy (control group) from hospital admission until hospital discharge or a maximum of 20 days.

In a pre-study pilot testing, the accuracy of the Dexcom G6 continuous glucose sensor during cardiac surgery with hypothermic extracorporeal circulation (ECC) will be evaluated in 15 adults. Accuracy results will influence the need and frequency for blood glucose blood glucose monitoring in cardiac surgery patients receiving closed-loop insulin therapy.

Methods of minimising bias

6.1.1 Randomisation

Randomisation will be done using the minimisation method, generated by the Minim randomisation software (*37*), which is a biased coin approach with a probability of 0.7-0.8 of allocation to the best fitting treatment. This method aims to minimise imbalance between groups. The allocation algorithm takes into consideration the characteristics of previously allocated participants to determine the best fitting treatment group. Randomisation will be stratified by HbA1c (<7.5 or ≥7.5 %) and, pre-study total daily insulin dose (<50 or ≥50 units/day).

6.1.2 Blinding procedures

Blinding of the study intervention/comparator is not feasible.

6.1.3 Other methods of minimising bias

The study outcome time spent for diabetes management will be assessed by a person who is not a member of the study team but knowledgeable about diabetes management including the use of novel technologies.

7. STUDY POPULATION

The study population will consist of adults with type 2 diabetes undergoing elective abdominal, thoracic, cardiovascular or other type of elective surgery at the University Hospital Bern.

Eligibility criteria

Participants fulfilling all of the following inclusion criteria will be eligible for the study:

- Written informed consent
- The subject is aged 18 years or over
- Diagnosis of type 2 diabetes using standard diagnostic practice (*38*) (not necessary for participation in the accuracy study)
- The subject is planned for an elective abdominal, thoracic, cardiovascular or other type of elective surgery at the University Hospital Bern expected to last ≥2 hours (cardiovascular surgery with the use of ECC for participation in the accuracy study)
- The subject requires treatment with subcutaneous insulin as part of the perioperative glucose management (not necessary for participation in the accuracy study)
- The subject is literate in German and/or French
- The subject is willing to wear study devices 24/7

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

- Physical or psychological condition likely to interfere with the normal conduct of the study and interpretation of the study results as judged by the investigator
- Known or suspected allergy to insulin
- Type 1 diabetes
- Pregnancy, planned pregnancy, or breast feeding
- Medically documented allergy towards the adhesive (glue) of plasters or unable tolerate tape adhesive in the area of sensor placement
- Lack of safe contraception for female participants of childbearing potential for the entire study duration (medically reliable method of contraception are considered oral, injectable, or implantable contraceptives, intrauterine contraceptive devices, or any other methods judged as sufficiently reliable by the investigator in individual cases).
- Serious skin diseases located at places of the body, which potentially are possible to be used for localisation of the glucose sensor
- Illicit drug abuse or prescription drug abuse
- Incapacity to give informed consent
- Droplet/airborne isolation precautions
- Participation in another clinical trial that interferes with the interpretation of the study results

Assignment to study groups

The randomisation will be done by a member of the study team within 72 hours of surgery. Assignment to the intervention or control group will be communicated to the participants on the day of hospital admission before commencement of study-related procedures.

Criteria for withdrawal / discontinuation of participants

The following withdrawal criteria will apply:

- The subject's behaviour interferes with a safe conduct of the study
- Decision by the treating clinical team that termination is in the subject's best medical interest
- Decision by the Sponsor-investigator that termination is in the subjects' best medical interest
- Allergic reaction to insulin or accessories of the study devices
- The subject wishes to terminate the study

Participants who are withdrawn from the study within ≤ 48 hours of hospital admission for the elective surgical procedures will be replaced. Subjects who discontinue the study intervention pre-maturely will receive an exit medical assessment.

Data of participants who withhold consent during the trial will continue to be used in coded form and cannot be anonymized, as indicated in the Informed Consent document.

8. METHODS UNDER INVESTIGATION

Description of the medical device under investigation

The medical device under investigation is the CE-marked CamAPS HX closed-loop system comprising:

- Dana insulin pump ® (Diabecare, Sooil, Seoul, South Korea)
- Dexcom G6 real-time CGM system ® (Dexcom, Northridge, CA, USA)
- An Android smartphone hosting CamAPS HX Application with the Cambridge model predictive control algorithm and communicating wirelessly with the insulin pump
- Cloud upload system to monitor CGM/insulin data

The intended purpose is automated day and night fully closed-loop insulin delivery to manage glucose levels in adults with type 2 diabetes in hospital. The application will be downloaded from the Amazon store using a study key that will be shared with the investigators. All commercial products will be used in line with their intended purpose according to the manufacturer's instruction. Study supplies will be kept in a secure, limited access storage area complying with the recommended storage conditions.

The closed-loop system consists of components directly attached to the patient, which are the CGM sensor/transmitter and the insulin pump. The measurement electrode of the CGM system is inserted into the subcutaneous tissue and stays in place with an adhesive tape worn on the skin. The transmitter with converts the electrical signal into a glucose concentration is placed onto a mount that is linked with the adhesive tape. The sensor requires replacement every 10 days whilst the transmitter has a life-time of 3 months. The DANA RS pump infuses insulin through a subcutaneous insulin infusion set that requires replacement every 2-3 days. The insulin reservoir of the pump can contain up to 300 units of insulin. The component not directly attached to the participant is the handheld smartphone containing closed-loop algorithm and communicating wirelessly with the insulin pump. The CamAPS HX closed-loop system is initialised using the participant's body weight and estimated total insulin dose. The CamAPS HX closed-loop system consists of a model predictive control algorithm that adapts itself to a particular patient by updating model parameters and refining the patient's insulin requirements. The insulin infusion rate is re-evaluated every 10-12 minutes on the basis of sensor glucose measurements. The algorithm's glucose target can be customized with the default setting being 5.8mmol/L. Safety rules limit maximum insulin infusion and suspend insulin delivery at a sensor glucose measurement of 4.2mmol/L or less, or when sensor glucose is rapidly decreasing. The system does not require administration of meal boluses or announcement of meals. In the event of sensor failure or loss of sensor availability, the study pump insulin infusion rate reverts to the pre-programmed basal rate after 70 minutes. For longer interruptions of sensor glucose data, the control algorithm can use capillary glucose levels to direct insulin delivery.

Insulin aspart to fill the study pump will be purchased from the hospital pharmacy. None of the study devices (CGM system, study pump, smart phone) are compatible with magnetic resonance imaging procedures.

Description of the comparator

The control group will receive insulin therapy in accordance with local practice. The insulin regimen during the study period may involve subcutaneous and/or insulin intravenous insulin administration. The modality of insulin treatment, dose adjustment and frequency of glucose monitoring will be at the discretion of the clinical team. No active treatment optimisation will be undertaken by the study team. Participants in the control group will be fitted with the identical study Dexcom G6 ® CGM system on the day of hospital admission but will wear a receiver device instead of a smartphone which will be modified to mask the sensor glucose values to the participant, investigators, and hospital staff.

Required training

Prior to commencement of the study, the research team consisting of nurses and clinicians will be trained to use closed-loop system and its components. Completed training will be documented in the Trial Master File.

Accountability of the methods under investigation

The Sponsor-Investigator and local will ascertain that the investigational devices are used for the study purposes only. Devices will be identified using batch/lot/serial numbers and the location of investigational devices and

their dates of use by subjects will be documented throughout the study. Storage of devices and supplies will be performed in accordance with the manufacturer's instructions.

Concomitant glucose-lowering treatment

In the closed-loop group, participants' usual insulin therapy will be discontinued before the initialisation of closed-loop insulin delivery. With the exception of sulfonylurea medication, other non-insulin glucose lowering therapies can be continued or resumed during the course of the study according to the decision of the clinical team.

9. STUDY SCHEDULE AND PROCEDURE

Overview

The study will be coordinated by the Sponsor-Investigator's research team belonging to the Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism.

The study will consist of a screening visit performed during the routine pre-operative clinical assessment (taking place 1-4 weeks prior to the elective surgical procedure), an initialisation visit at hospital admission and a closing-visit on the day of hospital discharge. Randomisation will be performed within 72 hours prior to surgery. The study period for the assessment of outcomes in hospital will last a maximum of 20 days. During the study period, the participants will be regularly seen by the study team to check for maintenance of study devices and supplies and to screen for incidence of device intolerances (e.g. skin reactions). The study design is illustrated in Figure 1 and the schedule of study-related activities can be found in the appendix.

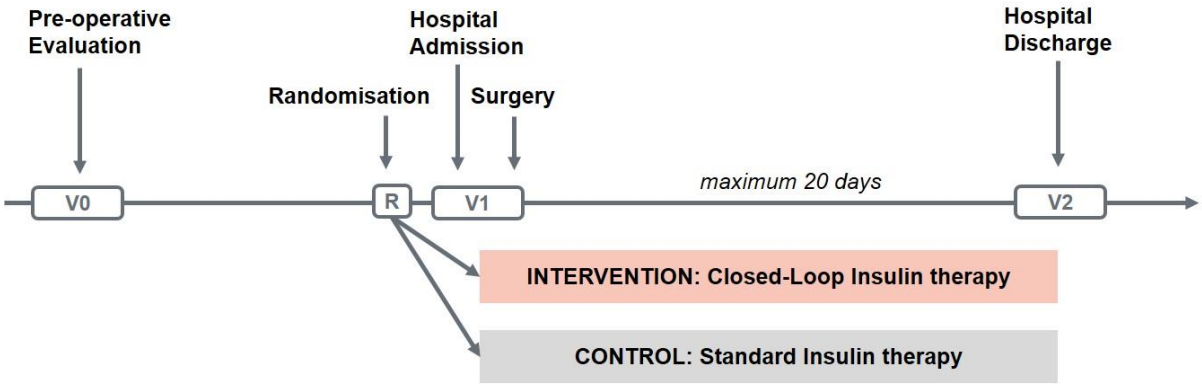

Figure 1. Study design and procedures.

Study procedures

9.1.1 Pre-study pilot-testing of sensor accuracy during hypothermic extracorporeal circulation

In a total of 15 patients undergoing cardiac surgery during hypothermic extracorporeal circulation (ECC) the accuracy of the Dexcom G6 continuous glucose sensor will be evaluated. Participants will be enrolled considering the eligibility criteria specified in section 7 except that type 2 diabetes or insulin treatment is not a requirement for participation. Eligible participants will be approached on the day before the planned cardiac surgery. Procedures will be explained and written informed consent will be obtained. A study sensor will be inserted on the right or left lumbar space. Upon start of the surgery, a reference blood glucose measurement will be performed every 20min using the Accu-Chek® Inform II System (Roche Diagnostics). Venous blood will be obtained from a central venous access that is used for peri-operative monitoring and treatment. The blood volume collected for each reference measurement is 1ml. Reference measurements will be stopped once the participant is discharged from the post-anaesthesia care unit or transferred to Intensive Care Unit. Wearing the sensor until hospital discharge will not have any implications on the routine clinical workflow in hospital. Sensor removal will be performed by a member of the study team.

9.1.2 Recruitment and screening visit

Potential participants will be identified by the treating surgeons or anaesthesiologists during the routine pre-operative visit and a contact with the study team will be established if agreed by the patient. The study team will re-evaluate the eligibility of referred patients and provide them with concise information about the purpose, design and procedures of the clinical trial on the day of the pre-operative visit. The study information sheet and consent form will be distributed. Written consent will be obtained on the same day or at a later time point before hospital admission to allow for a reflection period where required.

Participants will be provided with the study team's contact details (email and 24 hour study telephone helpline) in case any questions arise before the planned hospital admission.

Woman of child-bearing potential will be required to take a pregnancy test and will be advised to use safe contraception during study participation.

The number of approached patients who either refuse to participate in the trial or are not deemed suitable for participation by the treating physician or clinical investigator will be documented. In the latter case, the reason will be specified in line with the requirements for the CONSORT flow diagram.

9.1.1 Initialisation visit

Participants will be admitted to hospital early in the morning on the day of the scheduled surgical procedure. A member of the study team will meet the participant in the patient room on the wards and install the study devices. The body weight will be measured as part of admission medical check done by the ward staff and utilised for the initialisation of the closed-loop system. Approximately one hour later, the participant will be translocated to the pre-operative holding area for the induction of anaesthesia. The different clinical teams involved in the perioperative care of the participants in both groups will be informed about the study and that the prescription of blood glucose monitoring in both group and insulin therapy in the control will be under their control.

9.1.2 Regular contact during the hospital stay

Study participants will be regularly seen by the study team for the maintenance of study devices and supplies. These activities will include replacement of CGM sensors in both groups and changes of infusion sets and insulin reservoirs in the closed-loop group. Other reasons for contacts include technical trouble-shooting in the event of device deficiencies, assessment of safety events or the need to remove and re-install devices when participant need to undergo MRI procedures. Ward staff will provided with the study team's 24 hour telephone. If necessary, the participants' glucose control and insulin delivery profile can be remotely monitored by the study team.

Closed-loop glucose control and wearing of study devices may be transiently interrupted if needed for medical interventions (e.g. magnetic resonance imaging) or deemed necessary by the clinical team. Such instances will be considered study suspension periods and contribute to the maximum study period (20 days).

9.1.3 Closing visit

On the day of hospital discharge or after having worn study devices for 20 days, all study devices will be removed. Study participants in the closed-loop group will be transitioned to their usual glucose-lowering treatment modality by the study team. After study completion, optimisation of the participants' diabetes care will be offered by the study team to the clinical team for both groups.

Assessment of study outcomes

Measures of glucose control will be assessed using continuous glucose monitoring with data being downloadable from the cloud. Insulin requirements will be evaluated from pump insulin delivery data in the closed-loop group (downloadable from the cloud) or medical records in the control-group. Socio-demographic and clinical data will be derived from the medical records and conversation with the participants and treating physicians. Surgical details and post-operative comorbidity will be provided by the surgical teams and be retrievable from the medical records.

All study data will be collected in the study database RedCap® using electronic case report forms with manual

data entry or direct import of coded source data files. Coded continuous glucose monitoring data and insulin delivery data (closed-loop group only) will be exported from the Diasend platform and imported into the study database. Further imported data will include laboratory values and insulin prescription data from the electronic patient management system of the hospital. Socio-demographic variables, details about the participants' medical history, prescribed medication, post-operative comorbidity and safety events will be derived from the medical records and conversations with participants and treating physicians and directly entered into the study database.

Assessment of safety outcomes

Assessment of adverse event and other safety issues will be assessed by the study team during the regular contacts with participants and at the closing visit before hospital discharge. If an adverse occurs, the following information will be collected: time of onset, duration, resolution, action to be taken, assessment of intensity, relationship with study treatment.

10. SAFETY

Management of safety related events

Since the study will be performed in the perioperative hospital setting and involve comorbid patients undergoing complex surgeries, only unanticipated adverse events (AE), AE and device deficiencies relating to the study procedures will be fully investigated, documented in the electronic case report form (CRF) and considered for reporting. The period for the assessment of safety related events ranges from patient's written informed consent until the last protocol-specific procedure. Documentation includes dates of event, treatment, resolution, assessment of seriousness and causal relationship to device and/or study procedure [ISO 14155, 6.4.1.]. The information on AEs will be systematically collected by clinical safety assessments at the regular study visits. Participants will be followed-up until resolution of (serious) adverse events.

Definition of safety related events

10.1.1 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in participants, users or other persons whether or not related to the investigational medical device [ISO 14155: 3.2].

10.1.2 Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device [ISO 14155: 3.1].

10.1.3 Serious Adverse Event (SAE)

Any adverse event that led to any of the following [European regulation on medical devices 2017/745, art. 58]:

- death,
- serious deterioration in the health of the subject that resulted in any of the following:
    - life-threatening illness or injury,
    - permanent impairment of a body structure or a body function,
    - hospitalisation or prolongation of patient hospitalisation,
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
    - chronic disease,
- foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

10.1.4 Device deficiency

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labelling [ISO 14155: 3.15].

10.1.5 Health hazards that require measures

Findings in the trial that may affect the safety of study participants and, which require preventive or corrective measures intended to protect the health and safety of study participants SAE [ClinO Art. 37].

Anticipated adverse events/device effects

Anticipated adverse events/device effects include

- **Hypoglycaemia:** The risk is inherent to any form of insulin treatment and thus pre-existing in the study participants. The risk of hypoglycaemia due to participation in the trials is similar to the risk that an insulin-treated individual experiences on a daily basis. The study intervention represents a development to minimise the risk of hypoglycaemia. Mild to moderate hypoglycaemia manifests with symptoms such as sweating, trembling, difficulty thinking and dizziness. There is also a rare risk of severe hypoglycaemia when conscious level is altered, needing help from a third party to correct the hypoglycaemia.
- **Hyperglycaemia:** The risk of mild to moderate hyperglycaemia in the clinical trial is similar to the risk that an individual with type 2 diabetes has on a daily basis. Clinically significant hyperglycaemia with ketonaemia (beta-hydroxybutyrate>1.0 mmol/L) is rare in type 2 diabetes due to residual endogenous insulin production. If the closed-loop system is not active, it reverts to a pre-programmed infusion rate which delivers 20% of the participant's requirement to ensure prevention of ketosis. In the closed-loop group, steel cannulas will be used to diminish the risk of issues with subcutaneous insulin infusion.
- **Bruising and skin bleeding:** Insertion of study devices (CGM sensor and insulin infusion cannula) can lead to bruising or minor skin bleedings. These risks also exist with daily diabetes management in routine care (finger-stick blood glucose measurements, insulin injection therapy). Due to negligible health consequences, no specific mitigation measures are necessary.
- **Skin reactions:** The use of dressings and tapes may lead to irritative or allergic skin reactions which most commonly present with swelling, redness and itching. These reactions are usually mild and well-treatable by dechallenge. Severe skin reactions with systemic symptoms are extremely rare. Known allergies to adhesives and skin diseases are an exclusion criteria of trial participation. The risk of skin infections due to study procedures is rare.

Assessment of causal relationships

A causal relationship towards the medical device or study procedure will be rated as follows [MEDDEV 2.7/3 revision 3, May 2015]:

- **Not related:** The relationship to the device or procedures can be excluded.
- **Unlikely:** The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- **Possible:** The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible.
- **Probable:** The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause.
- **Causal relationship:** The serious event is associated with the investigational device or with procedures beyond reasonable doubt.

Reporting of safety related events

All SAEs, device deficiencies and health hazards that require measures will be reported to the Sponsor-Investigator within 24 hours upon becoming aware of the event. Device deficiencies will be assessed regarding their potential to lead to an SAE.

The Sponsor-Investigator will comply with the notification requirements specified in Art. 15 of the MedDO of 17 October 2011 (SR 812.213) and [ClinO Art. 37 and 42].

The below listed device-related safety events will be notified to the local centre of materiovigilance and to the Ethics Committee within the indicated time periods. Additionally, the manufacturer will be directly notified as specified in the trial agreement.

- Device deficiencies that could have led to serious adverse events if suitable action had not been taken, intervention had not been made, or circumstances had been less fortunate (time period: 7 days)
- Serious adverse events that are related to the study intervention (time period: 7 days)
- Health hazards that require measures will be reported to the Sponsor-Investigator (time period: 2 days)

All safety events (including those without a relationship to the study intervention) will be recorded in the eCRF and shared with the Ethics Committee Bern in the yearly safety update-report.

11. STATISTICAL METHODS

Hypothesis

The Null Hypothesis is that there is no difference in the true mean time spent in the target range (5.6 to 10.0 mmol/L) between the two treatment groups. The Alternative Hypothesis is that there is a nonzero difference in the true mean time spent in the target range between the two treatment groups.

Sample Size

The trial is designed to have a power of 80% to detect a clinically significant between-group difference in the primary outcome of 20 percentage points with the use of a two-sided t-test and an alpha level of 0.05. To reflect heterogeneity among the participants, a standard deviation of ±30% for the primary outcome was used for the power calculation. Thus the target sample size is 40 (n=20 in each group).

Sample size for the accuracy testing (n=15) was determined based on the anticipated amount of data pairs required to calculate standard performance metrics.

Planned Analyses

Efficacy data will be analysed according to the intention-to-treat principle. Analysis will be performed from the first available sensor reading of each intervention period until hospital discharge or day 20 counted from day of surgery. Data from all randomised participants with or without protocol violation including dropouts and withdrawals be included in the analysis.

Statistical analyses will be based on general linear modelling (GLM) methods using appropriate post-hoc techniques (e.g. for subgroup analyses) and Generalized Estimating Equations (GEE) methods in order to accommodate the longitudinal setting for time-varying outcome variables of interest. Standard descriptive statistics, and illustrative graphing will be used throughout, along with normality testing (e.g. Shapiro-Wilk) in order to check assumptions for the appropriate use of parametric testing approaches. Transformations to normality for variables not fulfilling normality assumptions will be considered (e.g. log, Box-Cox etc.), while nonparametric testing using counterparts of ad-hoc parametric procedures will also be an option as needed (e.g. Kruskal-Wallis instead of one-way ANOVA, the latter being part of the GLM family). IBM SPSS 26.0 (IBM Corp., Armonk, NY) and R (R Foundation for Statistical Computing, Vienna, Austria) will be used for data analysis. A test-wise 2-sided p-value of less than 0.05 (after post-hoc and/or FDR adjustment if deemed appropriate) will be considered statistically significant. All statistical analyses will be performed by the applicant's research team biostatistician and involve statistical counselling by the Clinical Trial Unit as needed.

11.1.1 Primary Analysis

The primary outcome measure is time spent with glucose concentration in the target range (5.6-10.0 mmol/L) during the study period based on continuous glucose monitoring (CGM) data.

For the primary outcome, a single value will be calculated for each subject for each treatment arm by pooling all CGM readings between the treatment initiation visit up to hospital discharge or 20 days.

11.1.2 Secondary Analyses

For all secondary endpoints, summary statistics appropriate to the distribution will be tabulated by treatment group. Analysis of secondary endpoints will parallel the primary analysis. A ranked normal score transformation will be applied to all highly skewed secondary endpoints.

Pilot-testing: Sensor performance during hypothermia will be analysed using standardised sensor accuracy metrics in line with previous research (*29*).

11.1.3 Interim analyses

No interim analysis is planned.

11.1.4 Safety analysis

Safety events will be tabulated in each trial group and the proportion of participants with events in each group will be compared with Fisher's exact test.

Handling of missing data and drop-outs

There will be no imputation for missing data. Drop-outs that occur within 48 hours after hospital admission will be replaced.

12. QUALITY ASSURANCE AND CONTROL

Data handling and record keeping / archiving

All study data will be collected and archived in a coded format in the study database with the exception of signed informed consent forms which will be stored in a locked cabinet.

12.1.1 Case Report Forms

Data will we recorded using electronic Case Report Forms (eCRFs). During the study, eCRFs will be kept up to date by the study team. CRFs are linked with participants' study ID. The study delegation log describes who will be authorized for eCRF entries. Once data collection is completed and validated, the Sponsor-Investigator will sign off all eCRFs.

12.1.2 Specification of source documents

The data management plan specifies what constitutes source data. In case CRFs are not serving as source documents, source documents will be retained for audit trail purposes. Location of source data is agreed in the data management plan.

Source data contain signed Informed Consent Forms, randomisation log of the Minim software, exports from the Diasend software (servers are located in the European Union) that hosts the continuous study data from devices, the study outlook calendar indicating the dates of study visits and all clinical and safety related data that is directly recorded in the eCRF (socio-demographic data, medical history, medication, details of the surgery, length of stay, comorbidity, safety evens and device issues).

12.1.3 Record keeping / archiving

All study data will be archived for a minimum of 10 years after study termination or premature termination of the clinical trial. Electronic data will be archived within the study database and paper-based documents (signed informed consent forms) within the Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism.

Data management

A study-specific data management plan defines the scope, standard operating procedures (SOPs) and the responsibilities for data management procedures within the present study.
Data management related to the certified medical device under investigation (CamAPS HX) was shown to comply will all data security standards during the approval process. CamAPS HX sends data directly to Diasend servers and also to its own servers. All servers are located in the European Unit.

12.1.4 Study Database

Study data will be collected and managed using REDCap electronic data capture tools hosted at the Department of Anaesthesiology and Pain Medicine, Inselspital, Bern University Hospital (68). REDCap® (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources [https://projectredcap.org/resources/citations/].

Data within REDCap® are stored in relational database engines like PostgreSQL or Microsoft SQL server. REDCap® provides web application security and can be configured for Secure Socket Layer (SSL) encrypted data transfer if needed. T

12.1.5 Data security, access and back-up

The study data base in REDCap® can only be accessed by designated investigator staff entering a user name and password. The application has a group and role-based security model. Each user belongs to one or more security groups with specific sets of permissions about folder or projects in the system. Only dedicated site administrators have access to the admin console, enabling user management and changing security settings.

All events are recorded in the user event list of the audit log files. Data are stored and visualised in data grids either in the format of datasets, lists or assays. Each change of data is tracked and documented in corresponding audit log files.

The servers are behind a firewall and cannot be accessed through the internet. They are located in locked dedicated server rooms with restricted access. Apache HTTP Server and REDCap® were configured to run under Secure Sockets Layer (SSL) which implies that data is encrypted and transmitted securely.

Available disk space is monitored actively. If free disk space is less than 10%, administrators get an email, and more storage capacity will be added accordingly.

All servers are regularly backed up on storage servers in a separate server room using a multi-level system.

12.1.6 Analysis and archiving

REDCap® provides data analysis by integrated tools for creating reports and charts. All data can be exported in different formats (Microsoft Excel, CSV, PDF, SAS, Stata, R, SPSS) suitable for transfer to a statistical software package of choice. All data will be archived and secured in the database at least 10 years.

12.1.7 Electronic and central data validation

An automatic validation program within RedCap® will check for data discrepancies and, by generating appropriate error messages, allow modification or verification of the entered data by the investigator staff.

Monitoring and study registration

The Sponsor-Investigator will ensure that the study is conducted in accordance with GCP through monitoring visits. Monitoring commensurate with size and complexity of the study consist of an initiation and a close-out by a qualified Monitor. Source data and all project related files and documents will be made accessible to monitors.

The study has been registered in the Swiss National Clinical Trial Portal (SNCTP) via BASEC. In addition, the study has been registered on clinicaltrials.gov (NCT04361799).

Audits and Inspections

In the event of audits and inspections, all the study documentation and the source data will be made accessible to auditors/inspectors.

Confidentiality, Data Protection

Each study participant will be assigned a study ID consisting of the study acronym and a two-digit number (POP_LOOP_XX). All collected data and specimens will be coded accordingly. The subject identification list will be kept in the Investigator Site File during the course of the clinical trial. After completion or termination of the study, the subject identification list will be kept by a person outside of the study team (Lars Wenzel, Department of Anaesthesiology and Pain Medicine). In case of further use of research data, the researchers in charge will not have access to the subject identification list.

Storage of biological material and related health data

No biological material will be collected during the study. Health-related data will be stored in study database for a minimum of 10 years as outlined above.

13. PUBLICATION AND DISSEMINATION POLICY

Insights provided by this study will be disseminated to scientists, health care professionals, study participants, patient societies, industry and policymakers. Data will be submitted for publication in internationally peer-reviewed scientific journals; members of the study team and collaborators will all be co-authors. The privacy of each subject and confidentiality of their information shall be preserved in reports and publication of data.

14. FUNDING AND SUPPORT

The study is supported by a Grant from the Helmut Horten Foundation and intramural grants of the Department of Anaesthesiology and Pain Medicine, University Hospital Bern.

15. INSURANCE

The present study has risk Category A and therefore does not require a study-specific insurance.

16. APPENDIX

Schedule of study activities and assessments

Time	Pre-surgery period	Day of hospital admission	During hospitalisation	Day of hospital discharge or day 20
Oral and written information about the study	+			
Written informed consent	+			
Eligibility screening	+			
Details of medical history and current diabetes treatment	+	+		
Randomisation	+	+		
Installation of study devices	+	+		
Maintenance of study devices			+	
Collection of details related to daily diabetes management			+	
Assessment of time spent on diabetes management		+	+	

Removal of study devices, data download and import to RedCap database				+
Assessment of length of stay and Clavien Dindo Grading				+
Safety evaluation	+	+	+	+

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