BMJ Open

Dual hormone fully closed loop in type 1 diabetes: a randomised trial in the Netherlands – study protocol

Milena Jancev ,[1] Frank J Snoek,[2] Geert W J Frederix,[3] Heleen Knottnerus,[4] Helga Blauw,[5] Maureen Witkop,[5] Karel G M Moons,[3] Arianne C van Bon,[6] J Hans DeVries,[7] Erik H Serné,[8] Thomas T van Sloten,[1] Harold W de Valk,[1] for the DARE study consortium

To cite: Jancev M, Snoek FJ, Frederix GWJ, *et al*. Dual hormone fully closed loop in type 1 diabetes: a randomised trial in the Netherlands – study protocol. *BMJ Open* 2023;**13**:e074984. doi:10.1136/bmjopen-2023-074984

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-074984).

ACvB, JHD, EHS, TTvS and HWdV contributed equally.

This abstract was presented during the Advanced Technologies & Treatments for Diabetes conference (ATTD) in February 2023 in Berlin, Germany. Another version of the abstract was presented at the Annual Dutch Diabetes Research Meeting (ADDRM), on 3rd November 2022 in Wageningen, The Netherlands.

Received 22 April 2023
Accepted 08 August 2023

For numbered affiliations see end of article.

Correspondence to
Dr Thomas T van Sloten;
t.t.vansloten@umcutrecht.nl

ABSTRACT

Introduction The management of type 1 diabetes (T1DM) has undergone significant advancements with the availability of novel technologies, notably continuous and flash glucose monitoring (CGM and FGM, respectively) and hybrid closed loop (HCL) therapy. The dual hormone fully closed loop (DHFCL) approach with insulin and glucagon infusion has shown promising effects in small studies on glycaemic regulation and quality of life in T1DM.

Methods and analysis The Dual Hormone Fully Closed Loop for Type 1 Diabetes (DARE) study is a non-commercial 12-month open-label, two-arm randomised parallel-group trial. The primary aim of this study is to determine the long-term effects on glycaemic control, patient-reported outcome measurements and cost-effectiveness of the DHFCL compared with usual care, that is, HCL or treatment with multiple daily insulin injections+FGM/CGM. We will include 240 adult patients with T1DM in 14 hospitals in the Netherlands. Individuals will be randomised 1:1 to the DHFCL or continuation of their current care.

Ethics and dissemination Ethical approval has been obtained from the Medical Research Ethics Committee NedMec, Utrecht, the Netherlands. Findings will be disseminated through peer-reviewed publications and presentations at local, national and international conferences.

Trial registration number NCT05669547.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is the first long-term (12 months) trial investigating the effectiveness of the dual hormone closed loop concept.
⇒ We will evaluate both glycaemic outcomes and patient-reported outcomes.
⇒ A cost-effectiveness analysis will be performed possibly giving more insight into implementing dual hormone closed loop concepts in daily diabetes practice.
⇒ The scope of this study is limited to adult individuals only.

INTRODUCTION

In previous years, there have been many technological advancements in type 1 diabetes (T1DM) management. These include continuous and flash glucose monitoring (CGM and FGM, respectively) and hybrid closed loops (HCLs).[1 2] Advanced HCLs automatically adjust basal insulin rates in anticipation to hypoglycaemia or hyperglycaemia and thereby prevent nocturnal hypoglycaemia and hyperglycaemia, while also administering correction doses.[3] These systems use insulin only and still require carbohydrate counting for administering mealtime insulin boluses. In contrast, the newly developed dual hormone fully closed loops (DHFCLs) provide a balanced infusion of not only insulin but also glucagon mimicking physiological conditions.[4–7] The user does not have to provide any meal or correction boluses as the DHFCL reactively adapts the insulin and glucagon infusion.[5] This removes any diabetes management burden related to meals or exercise. Patients using HCLs have achieved mean time-in-ranges (TIRs) ranging from 72.0% to 79.2%.[8–11] Blauw *et al* showed a median TIR of 86.6% in patients using a DHFCL with lower time in hypoglycaemia and hyperglycaemia in comparison with (sensor augmented) insulin pump treatment.[5] Though promising, DHFCLs are currently not commercially available and have only been tested in small patient groups (up to 39 patients) with limited follow-up time (up to 14 days).[6] Moreover, there is no information available yet on the costs of use of DHFCLs in regular diabetes care.[6] Here we describe the design of the Dual Hormone Fully Closed Loop in Type 1 Diabetes: a randomised trial (DARE study). The primary aim of this study is to determine the long-term effects of the DHFCL on glycaemic control, patient-reported outcomes (PROMs) and cost-effectiveness in comparison with the currently most advanced

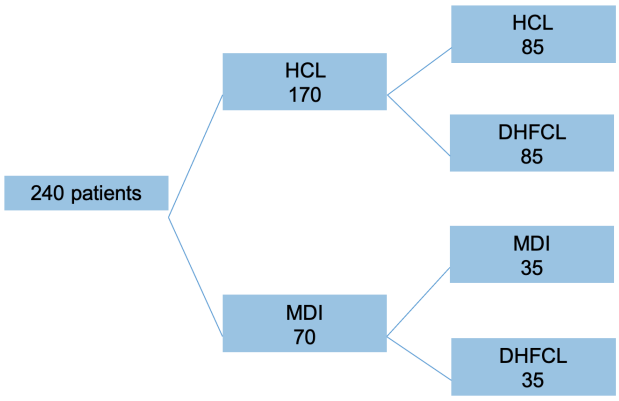

Figure 1 Patients on an HCL (n=170, advanced care) and MDI in combination with FGM or CGM (n=70, usual care) (total n=240) will be included in this trial. In both arms, patients will be randomised 1:1 to receive the intervention or continue their current care (control). CGM, continuous glucose monitoring; DHFCL, dual hormone fully closed loop; FGM, flash glucose monitoring; HCL, hybrid closed loop; MDI, multiple daily insulin injections.

technological care (ie, HCL) and the current usual care (ie, multiple daily insulin injections (MDI)+FGM/CGM).

METHODS

Study design

This is a non-commercial 12-month open-label, two-arm randomised parallel-group trial conducted in 14 centres in the Netherlands, both academic and regional. The study is funded by the Dutch governmental National Health Care Institute. One arm consists of HCL users (most advanced care). The other arm comprises patients on MDI treatment (at least one time per day long-acting insulin and three times per day short-acting insulin; most used care) with CGM or FGM (figure 1). In both arms, patients will be randomised 1:1 to continuation of their current care or use of the DHFCL.

Recruitment

Subjects will be recruited from the outpatient clinics in the participating centres starting from 1 August 2023. We aim to include all patients within 6 months after the first inclusion. Expected end date of the study is 1 February 2025. Informed consent will be obtained prior to any trial related visits in accordance with Good Clinical Practice (GCP) guidelines.

Study population

A total of 240 adult patients with T1DM aged 18–75 years will be included who are on an MDI schedule in combination with FGM/CGM or use an HCL for at least 3 months. Patients are required to have a glycated haemoglobin (HbA1c)≤91 mmol/mol (≈10.5%) and a TIR<80% or time-below-range (TBR)>4% in 8 weeks before screening. Patients who are using a non-approved HCL device, have a body mass index >35 kg/m^2 or have an estimated glomerular filtration rate <30 mL/min/1.73 m^2 will be excluded. Moreover, pregnant women are excluded. Full inclusion and exclusion criteria are presented in table 1.

Study plan

This outpatient trial has six visits (screening, baseline and at 3, 6, 9 and 12 months). Trial activities are described in the online supplemental appendix 2. Briefly, after screening, baseline data are collected. A blinded sensor (FreeStyle Libre Pro IQ, Abbott, USA) is placed for collecting glucose data, that is, TIR, time-above range (TAR) and TBR. The minimum required blinded sensor data is 50% (ie, 168 hours). In addition, at each study visit, online questionnaires are sent to the patient to be filled out at home. At the 3-month, 6-month, 9-month and 12-month visits, data are collected on (serious) adverse events, device issues, patient-reported daily insulin use, unplanned contact moments, medication use, glucose levels using a blinded sensor (FreeStyle Libre Pro IQ, Abbott, USA) and the PROMs in both the intervention and control group.

DHFCL and training

The DHFCL in this trial has been developed by Inreda Diabetic B.V. (Goor, the Netherlands). This Conformité Européene (CE) marked device is a wearable device integrating two pumps (for insulin and glucagon) and an algorithm, with two sensors and two infusion sets (for insulin and glucagon) that results in fully automated glycaemic control without the need—or possibility—for meal or correction boluses.[5] The device is not commercialised yet. At the start, Inreda Diabetic provides patients with a 1-day DHFCL training and (telephone) guidance in the first 8 weeks. After these 8 weeks, patients will receive routine support from their diabetes team in the participating centres. Patients will replace the pump glucagon (Glugon, United Biotech) each day during use of the DHFCL.

Questionnaires (PROMs)

At the baseline and subsequent visits, a link to the questionnaires (see online supplemental appendix 3) will be sent to the participating patients via email. The questionnaires cover multiple aspects of the participants' quality of life including general well-being, (fear of) hypoglycaemia, diabetes treatment satisfaction, sleep and expectations regarding use of insulin delivery systems (online supplemental appendix 3). In addition, the scores from the Medical Consumption Questionnaire (iMCQ) and Productivity Cost Questionnaire (iPCQ) are used for the cost-effectiveness analysis. Scoring of the questionnaires will be performed in accordance with the original articles.[12–22] Participants can fill out the questionnaires at their convenience. One automatic reminder will be sent through the electronic case report form if not completed within 4 days. Weekly, unfinished questionnaires will be monitored. If not completed, a maximum of two reminders will be sent (with a minimum interval

Table 1 Overview of patient inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
► Age between 18 and 75 years.	► Current use of non-approved HCL device.
► Diagnosed with type 1 diabetes mellitus at least 1 year ago.	► BMI>35 kg/m^2.
► HbA1c≤91 mmol/mol.	► eGFR<30 mL/min/1.73 m^2.
► Treated with either MDI with FGM/CGM or treated with HCL: – MDI+FGM/CGM for ≥3 months with an adequate sensor use during at least 70% of the time in the month prior to screening (based on sensor usage from the download summary report of the FGM/CGM). – HCL for ≥3 months with a frequency of use ≥70% of the time in auto mode over the previous month prior to screening.	► Plan to change usual diabetes regimen in the next 3 months.
► Not reaching the treatment goals over the last 8 weeks: – for MDI+FGM/CGM: subject has a TIR<80% or time-below-range (TBR)>4%. – for HCL: subject has a TIR<80% or TBR>4%.	► Current participation in another diabetes-related clinical trial.
► Willing to take or switch to insulin Humalog when randomised to the intervention DHFCL arm (the used DHFCL has only been tested with Humalog[5]).	► Actively participating in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or device in the last 2 weeks before enrolment into this study, as per investigator judgement.
► Under treatment in one of the participating centres.	► Established history of allergy or severe reaction to adhesive or tape that must be used in the study.
► Willing and able to sign informed consent.	► Use of oral glucose-lowering medication.
► Access to the internet at home (for DHFCL data upload).	► Active retinopathy or painful neuropathy.
	► Daily use of acetaminophen during the trial (all arms), as this may influence the sensor glucose measurements. Incidental use with a maximum of, for example, three daily doses of 1000 mg paracetamol for a maximum of three consecutive days is allowed.
	► Limited ability to see, hear or feel alarm signals of the closed loop system.
	► Current pregnancy, breast feeding or planning to become pregnant in the 12 months of the trial or using ineffective birth control methods.
	► Presence of a medical or psychiatric condition, longstanding serious adherence problems, anticipated problems in handing over diabetes control to a device or use of a medication that, in the judgement of the investigator, clinical protocol chair or medical monitor, could compromise the results of the study or the safety of the participant.

BMI, body mass index; CGM, continuous glucose monitoring; DHFLC, dual hormone fully closed loop; eGFR, estimated glomerular filtration rate; FGM, flash glucose monitoring; HbA1c, glycated haemoglobin; HCL, hybrid closed loop; MDI, multiple daily insulin injections; TIR, time-in-ranges.

of 4 days). Two weeks after the initial invitation, the questionnaires will be closed and reported as missing data in case the questionnaires have not been completed.

ENDPOINTS

The primary endpoint is the proportion of time spent in the TIR (3.9–10 mmol/L (70–180 mg/dL)) at 12 months. Secondary glycaemic control endpoints include the TAR (level 1 hyperglycaemia >10.0 mmol/L (180 mg/dL) and level 2 hyperglycaemia >13.9 mmol/L (250 mg/dL)), the TBR (level 1 hypoglycaemia <3.9 mmol/L (70 mg/dL) and level 2 hypoglycaemia: <3.0 mmol/L (54 mg/dL)), the number of hypoglycaemic events (defined as glucose <3.0 mmol/L for 15 consecutive minutes), the time in tight range (3.9–7.8 mmol/L) (70–140 mg/dL), the mean glucose (at day or night and combined), the

glycaemic variability (coefficient of variation and SD), the mean HbA1c, the percentage patients achieving HbA1c≤53 mmol/mol (7%), the percentage achieving TIR>70% or TBR<4% and the percentage patients with ≥5% points improvement from baseline (%) at 12 months. For the cost-effectiveness analysis, results from the iMCQ and iPCQ at 0, 3, 6, 9 and 12 months will be evaluated. Information on detailed hospital healthcare consumption for each individual patient (collected from electronic patient files, including unplanned additional contact moments) will be used to calculate cost per quality-adjusted life year (QALY). We will examine the PROMs using the questionnaire scores at the predefined intervals. Additionally, we assess the daily insulin use, DHFCL outcomes and safety outcomes. Finally, the continuation rate expressed as the percentage of participants that continue DHFCL treatment after 1 year of use and reasons for discontinuation of the DHFCL treatment will be evaluated. All study endpoints are summarised in online supplemental appendix 4.

STATISTICAL CONSIDERATIONS

Sample size calculation

The DHFCL is compared with two different control treatments in two separately randomised study arms.

Study arm with HCL as control treatment

Previous studies show a mean TIR with HCL treatment of 70% (SD 16–17%).[23–25] A recent small cross over study of the index intervention treatment (DHFCL) showed a median TIR of 86%.[5] To be conservative, assuming a 7% increase in mean TIR from 78% under the HCL control treatment to 85% under the index intervention treatment, the required sample size for this arm is around 68 per group (two sample t-test with unequal variance, two-sided significance level of 0.05 and a power of 90%). To allow for potential loss to follow-up and sufficient statistical power to address the main secondary endpoints we estimated a required sample size of 85 per group.

Study arm with MDI+FGM/CGM as control treatment

Previous studies show a mean TIR under MDI+FGM/CGM treatment of 50–59% (SD of 12–20%).[26] However, to be conservative we assume a mean TIR in the MDI+FGM/CGM control group of 70% and for the index intervention of 85%, thus assuming a 15% increase in mean TIR due to the intervention treatment. Based on that effect size, the required sample size for this arm is 22 per group (two sample t-test with unequal variance; two-sided significance level of 0.05; power of 90%). Similar to the HCL group, to allow for potential loss to follow-up and sufficient statistical power we estimated a required sample size of 35 per group.

Statistical analyses

Primary endpoint

The primary endpoint will be compared between the DHFCL treatment and each of the two control treatments separately, using linear regression modelling, assuming a normal distribution. In case of non-normal distribution, transformed TIR (to obtain a normal distribution) will be used as an outcome. The stratification factor for randomisation (centre) will be used as covariate in this analysis. The difference in mean TIR at 12 months between the index intervention treatment and each of the two control treatments will be calculated with the 95% CI. Subsequently, we will repeat this analysis by adjusting for a limited number of a priori defined prognostic factors of TIR at 12 months, that is, baseline TIR (which is blinded for outcome assessors), age and gender. This analysis will be performed on the intention-to-treat principle, but also on a per-protocol principle.

A secondary analysis of the primary endpoint will be performed using random effects multilevel modelling to account for the nested and longitudinal structure of the primary endpoint data over the full 12 months follow-up. This analysis provides insight into the change of mean TIR over time, compared between the intervention and each of the control treatments.

Secondary endpoints

The analysis for continuous secondary outcomes follows the analysis strategy of the primary outcome. Binary secondary outcomes will be compared using relative risk estimates with 95% CI in which the stratification factor for randomisation (centre) will be used as covariate. Subsequently, as for the analysis of the continuous endpoints, a multivariable logistic regression analysis will be performed by adjusting for the same a priori defined prognostic factors as above.

QALYs will be calculated and described using means with 95% CI, and indirect costs will be calculated and described using medians and IQRs, and also means with 95% CI based on bootstrapping, separately per group. Incremental cost-effectiveness ratios will be calculated with both probabilistic and deterministic sensitivity analysis to outline uncertainty on outcome measures.

ETHICS AND DISSEMINATION

Ethics

Ethical approval has been granted by the Medical Research Ethics Committee NedMec Utrecht, the Netherlands (study ID 22–671).

Safety and data protection

Data collection is managed by GCP trained and experienced research staff. Data will be stored securely and in compliance with the latest European General Data Protection Regulation privacy guidelines. A data safety monitoring board will monitor evidence for harm (adverse

events and serious adverse events) of the intervention being studied.

Dissemination

We will communicate the study findings to the scientific community via international peer-reviewed scientific journals and present the data at (inter)national conferences. We will also communicate the output to policymakers. Results of this study will be taken into account for decision making by the Dutch National Health Care Institute regarding the reimbursement of DHFCL concepts in the Netherlands.

PATIENT AND PUBLIC INVOLVEMENT

A patient representative of the Dutch Diabetes Association (HK) was involved during the conceptualisation of the study. She is a member of the study steering committee and remains actively involved throughout the study's conduct.

Author affiliations
[1]Vascular Medicine and Endocrinology, UMC Utrecht, Utrecht, The Netherlands
[2]Medical Psychology, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands
[3]Epidemiology & Health Economics, Julius Center for Health Sciences and Primary Care, UMC Utrecht, Utrecht University, Utrecht, The Netherlands
[4]Dutch Diabetes Association, Amersfoort, The Netherlands
[5]Inreda Diabetic, Goor, The Netherlands
[6]Department of Internal Medicine, Rijnstate Hospital, Arnhem, The Netherlands
[7]Internal Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
[8]Internal Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

Acknowledgements We would like to thank the National Health Care Institute and ZonMw for providing funding for this trial.

Collaborators T van Bemmel (Department of Internal Medicine, Gelre Hospital, Apeldoorn, The Netherlands); C B Brouwer (Department of Internal Medicine, OLVG, Amsterdam, The Netherlands); P R van Dijk (Department of Internal Medicine, UMC Groningen, Groningen, The Netherlands); L T Dijkhorst-Oei (Department of Internal Medicine, Meander Medical Centre, Amersfoort, The Netherlands); K Hoogenberg (Department of Internal Medicine, Martini Hospital, Groningen, The Netherlands); F A W Kemperman (Department of Internal Medicine, Jeroen Bosch Hospital, Den Bosch, The Netherlands); L P Klieverik (Department of Internal Medicine, St. Antonius Hospital, Nieuwegein, The Netherlands); M M Oosterwerff (Department of Internal Medicine, Catharina Hospital, Eindhoven, The Netherlands); E Seebus (Department of Internal Medicine, Tergooi Hospital, Hilversum, The Netherlands); S E Siegelaar (Department of Internal Medicine, Amsterdam UMC – AMC, Amsterdam, The Netherlands); T M Vriesendorp (Department of Internal Medicine, Isala Hospital, Zwolle, The Netherlands).

Contributors MJ: writing—original draft, methodology. FJS: conceptualisation, methodology. GWJF: conceptualisation, methodology. HK: conceptualisation, methodology. HB: conceptualisation, resources. MW: conceptualisation, resources. KGMM: conceptualisation, methodology, review and editing. ACvB: conceptualisation, methodology. JHD: conceptualisation, methodology, review and editing. EHS: conceptualisation, methodology, review and editing. TTvS: methodology, review and editing. HWdV: conceptualisation, methodology, review and editing.

Funding This study is fully funded by the Promising Care programme from the Dutch National Health Care Institute/ZonMw.

Competing interests HB and MW are employees of Inreda Diabetic B.V., which supplied the bihormonal devices.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Patient and public involvement section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Milena Jancev http://orcid.org/0000-0002-5193-8459

REFERENCES

1 Sherr JL, Heinemann L, Fleming GA, *et al*. Automated insulin delivery: benefits, challenges, and recommendations. A consensus report of the joint diabetes technology working group of the European Association for the study of diabetes and the American Diabetes Association. *Diabetologia* 2023;66:3–22.
2 Holt RIG, DeVries JH, Hess-Fischl A, *et al*. Management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the study of diabetes (EASD). *Diabetes Care* 2021;44:2589–625.
3 Infante M, Baidal DA, Rickels MR, *et al*. Dual-hormone artificial pancreas for management of type 1 diabetes: recent progress and future directions. *Artif Organs* 2021;45:968–86.
4 Blauw H, van Bon AC, Koops R, *et al*. Performance and safety of an integrated bihormonal artificial pancreas for fully automated glucose control at home. *Diabetes Obes Metab* 2016;18:671–7.
5 Blauw H, Onvlee AJ, Klaassen M, *et al*. Fully closed loop glucose control with a bihormonal artificial pancreas in adults with type 1 diabetes: an outpatient, randomized, crossover trial. *Diabetes Care* 2021;44:836–8.
6 Zeng B, Jia H, Gao L, *et al*. Dual-hormone artificial pancreas for glucose control in type 1 diabetes: a meta-analysis. *Diabetes Obes Metab* 2022;24:1967–75.
7 El-Khatib FH, Balliro C, Hillard MA, *et al*. Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicentre randomised crossover trial. *Lancet* 2017;389:369–80.
8 Da Silva J, Bosi E, Jendle J, *et al*. Real-World performance of the Minimed 670G system in Europe. *Diabetes Obes Metab* 2021;23:1942–9.
9 Brown SA, Forlenza GP, Bode BW, *et al*. Multicenter trial of a tubeless, on-body automated insulin delivery system with customizable glycemic targets in pediatric and adult participants with type 1 diabetes. *Diabetes Care* 2021;44:1630–40.
10 Silva JD, Lepore G, Battelino T, *et al*. Real-world performance of the Minimed™ 780G system: first report of outcomes from 4120 users. *Diabetes Technol Ther* 2022;24:113–9.
11 Pinsker JE, Müller L, Constantin A, *et al*. Real-world patient-reported outcomes and glycemic results with initiation of control-IQ technology. *Diabetes Technol Ther* 2021;23:120–7.
12 Topp CW, Østergaard SD, Søndergaard S, *et al*. The WHO-5 well-being index: a systematic review of the literature. *Psychother Psychosom* 2015;84:167–76.
13 Euroqol - a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
14 Bradley C, Lewis KS. Measures of psychological well-being and treatment satisfaction developed from the responses of people with tablet-treated diabetes. *Diabet Med* 1990;7:445–51.
15 Welch GW, Jacobson AM, Polonsky WH. The problem areas in diabetes scale: an evaluation of its clinical utility. *Diabetes Care* 1997;20:760–6.
16 Cox DJ, Irvine A, Gonder-Frederick L, *et al*. Fear of hypoglycemia: quantification, validation, and utilization. *Diabetes Care* 1987;10:617–21.

17 Buysse DJ, Reynolds CF, Monk TH, *et al*. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
18 Weissberg-Benchell J, Shapiro JB, Hood K, *et al*. Assessing patient-reported outcomes for automated insulin delivery systems: the psychometric properties of the INSPIRE measures. *Diabet Med* 2019;36:644–52.
19 Clarke WL, Cox DJ, Gonder-Frederick LA, *et al*. Reduced awareness of hypoglycemia in adults with IDDM: a prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care* 1995;18:517–22.
20 Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. *Diabetes Care* 1994;17:697–703.
21 Bouwmans C, Krol M, Severens H, *et al*. The iMTA productivity cost questionnaire: a standardized instrument for measuring and valuing health-related productivity losses. *Value Health* 2015;18:753–8.
22 iMTA Productivity and Health Research Group. *Manual iMTA Medical Cost Questionnaire (iMCQ)*. Rotterdam, 2018. Available: https://www.imta.nl/questionnaires/imcq/
23 Bergenstal RM, Nimri R, Beck RW, *et al*. A comparison of two hybrid closed-loop systems in adolescents and young adults with type 1 diabetes (FLAIR): a multicentre, randomised, crossover trial. *Lancet* 2021;397:208–19.
24 Brown SA, Kovatchev BP, Raghinaru D, *et al*. Multicenter trial of closed-loop control in type 1 diabetes. *N Engl J Med* 2019;381:1707–17.
25 Amadou C, Franc S, Benhamou P-Y, *et al*. Diabeloop DBLG1 closed-loop system enables patients with type 1 diabetes to significantly improve their glycemic control in real-life situations without serious adverse events: 6-month follow-up. *Diabetes Care* 2021;44:844–6.
26 Visser MM, Charleer S, Fieuws S, *et al*. Comparing real-time and intermittently scanned continuous glucose monitoring in adults with type 1 diabetes (ALERTT1): a 6-month, prospective, multicentre, randomised controlled trial. *Lancet* 2021;397:2275–83.