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Effectiveness of 6 months hybrid closed-loop insulin delivery on glucose control, psychosocial well-being, sleep and cognition in adults with type 1 diabetes: a randomised controlled trial protocol

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ABSTRACT

Introduction

Manual determination of insulin dosing largely fails to optimise glucose control in type 1 diabetes. Automated insulin delivery via closed-loop systems has improved glucose control in short-term studies. Longer-term home-based studies of closed-loop system effects on glucose, psychosocial well-being, sleep and cognition are merited.

Methods and analysis

This open-label, seven-centre, randomised controlled parallel group clinical trial will compare home-based hybrid closed-loop versus standard diabetes therapy in Australia. One hundred and twenty adults aged ≥25 years with type 1 diabetes using intensive insulin therapy (*n*=60 via multiple daily injections; *n*=60 via insulin pump) will undertake a run-in period including diabetes and carbohydrate-counting education, clinical optimisation and baseline data collection. Participants will then be randomised 1:1 either to 26 weeks of MiniMed™ 670G hybrid closed-loop system therapy (Medtronic, Northridge, CA, USA) or continuation of their current diabetes therapy. The hybrid closed-loop system delivers insulin automatically to address basal requirements and correct to target glucose level, while bolus doses for meals require user initiation and carbohydrate estimation. Analysis will be intention-to-treat, with the primary outcome time in continuous glucose monitoring (CGM) target range (3.9–10.0 mmol/L) during the final 3 weeks of intervention. Secondary outcomes include: other CGM parameters, HbA_{1c}, severe hypoglycaemia, psychosocial well-being, sleep, cognition, electrocardiography, costs, quality of life, biomarkers of vascular health and hybrid closed-loop system performance. Semi-structured interviews will assess the expectations and experiences of a sub-group of hybrid closed-loop users.

Ethics and dissemination

The study has Human Research Ethics Committee approval. The study will be conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Results will be disseminated at scientific conferences and via peer-reviewed publications.

Trial registration number

ACTRN12617000520336, pre-results

Strengths and limitations of the study

- Multi-centre, randomised controlled parallel group trial of 26 weeks home-based hybrid closed-loop versus standard therapy
- The study emphasises education and clinical optimisation for all participants pre-randomisation, and the visit schedule is identical for both groups
- Broad outcomes will be assessed in addition to glucose control: psychosocial, sleep, cognition, electrocardiography, vascular health biomarkers and health economic measures
- The standard therapy comparator includes either multiple daily insulin injections or insulin pump therapy while excluding real-time continuous glucose monitoring, thereby reflecting current practice in Australia for most adults with type 1 diabetes
- This study of adults aged ≥25 years has glucose end-points aligned with a concurrent study examining hybrid closed-loop for 12 to <25 year-olds, thereby facilitating comparison of metabolic outcomes between the two populations

INTRODUCTION

Advances in type 1 diabetes insulin regimens and glucose monitoring have occurred over recent decades, facilitating improved glucose control and resulting in better health and quality of life.[1-4] The long-term vascular complications of type 1 diabetes are reduced by intensive insulin therapy compared with less intensive therapy.[1 2] Consequently, intensive insulin therapy—with subcutaneous administration via either multiple daily injections (MDI) or insulin pump therapy (IPT)—is a core strategy in current type 1 diabetes management.[5] Nevertheless, even with modern therapies, only 20–30% of adults with type 1 diabetes achieve HbA_{1c} targets[6 7], and long-term vascular complications and reduced life expectancy continue to be a reality for people with type 1 diabetes.[8 9]

Insulin requirements can vary unpredictably. They are impacted by time of day, meals, exercise, illness and antecedent hypoglycaemia. Manual determination of insulin dosing by people with type 1 diabetes requires continuous vigilance to maintain glucose levels within a healthy range. Insulin dosing decisions carry cognitive and emotional burden, and may be inconsistent due to fatigue, distress, fluctuating glucose levels or coexistent fear of hypoglycaemia. Hence, manual determination of insulin dosing represents an imperfect strategy to optimise glucose control. Further advances in technology are required to improve the match of insulin delivered to individuals' varying insulin requirements, and to minimise the burden of type 1 diabetes.

Closed-loop systems are designed to maintain glucose levels at a predetermined target by linking continuous glucose monitoring (CGM) information with an insulin dosing algorithm for automated subcutaneous insulin delivery by a pump.[10] These systems are being developed to address the need for improving glucose control while reducing the burden associated with treatment regimens. There is increasing scientific literature reporting improved glucose control with short-term use of closed-loop systems (up to 3 months) compared with conventional insulin pumps.[11-14] A recent meta-analysis of outpatient randomised controlled trials with intervention periods ranging from 4 days to 12 weeks reported that single-hormone (insulin alone) closed-loop systems improve time-in-target glucose range and reduce time spent in hypoglycaemia compared with conventional IPT (with/without CGM).[15] Overall, time-in-target glucose range had a mean (95% confidence interval) absolute increase of 11.1% (6.9, 15.2), and the time spent in hypoglycaemia had an absolute reduction of 1.9% (0.4, 3.4). Studies in this meta-analysis used 'hybrid closed-loop' systems with automated insulin delivery to address basal requirements and correct to target glucose, and user-initiated

bolus insulin to address carbohydrate consumption. Results from a short-term randomised crossover study challenging a closed-loop system with both moderate- and high-intensity exercise indicated that closed-loop glucose control was safe; only a single episode of mild hypoglycaemia occurred and marked hyperglycaemic excursions were limited.[16]

For individuals with type 1 diabetes, both hypoglycaemia and hyperglycaemia can affect physical and emotional well-being, quality of life, and activities of daily living such as driving.[4 17-19] Moreover, type 1 diabetes places significant burden on caregivers, families, workplaces and health services.[20-22] Closed-loop technology has shown promise to address the limitations of current therapy in relation to these burdens.[23]

HbA_{1c}, a measurement of average glycaemia during the preceding 10–12 weeks, predicts the risk of developing long-term complications and is valuable for assessing glycaemic trends in populations over time.[1 2 24] However, HbA_{1c} cannot provide information about glucose variability or time-in-target glucose range, and is even considered an unreliable indicator of an individual's mean glucose.[25] A recent large longitudinal registry study reported lower cardiovascular and all-cause mortality in individuals using IPT compared with MDI, even without between-group differences in HbA_{1c}.[26] The mortality difference observed may have been attributable to factors such as time-in-target glucose range or glucose variability (not reflected in HbA_{1c}). Consequently, HbA_{1c} may be of limited value in comparison with CGM when assessing an individual's glucose levels in response to automated closed-loop insulin delivery.

With short-term studies of closed-loop systems (conducted in controlled and home settings) demonstrating improvements in glucose control,[15] it remains to be determined whether these findings are sustained in the longer term in the home setting and whether diabetes-related vascular complications may be influenced. Longer-term home-based studies—with closed-loop implemented day and night—are required. In addition, the impact of closed-loop insulin delivery on patient-reported outcomes such as fear of hypoglycaemia, treatment satisfaction, sleep quality and cognition remains a significant gap in the evidence base.[27] Finally, the benefits associated with this new technology need to be balanced against its cost.

In Australia, the government presently subsidises the purchase of insulin, injection needles, blood glucose monitoring strips and insulin pump delivery consumables for people with type 1 diabetes.[28] Insulin pumps are not government-subsidised, but are available via either direct purchase or in conjunction with a private health insurance fund. CGM is government-

subsidised only for eligible individuals under 21 years of age.[29] As a result, only a small fraction of adults with type 1 diabetes use CGM on a regular basis. Hence, standard diabetes therapy for adults in Australia currently involves subcutaneous intensive insulin therapy delivered via either MDI or pump, together with finger-prick blood glucose monitoring.

We hypothesise that hybrid closed-loop insulin delivery compared with manual insulin dosing will improve glucose control and non-glucose outcomes for adults with type 1 diabetes. The overall aim of the study is to evaluate the effectiveness of 6 months of hybrid closed-loop insulin delivery on glucose control, psychosocial well-being, sleep quality, cognition and markers of vascular disease risk compared with standard diabetes therapy for adults with type 1 diabetes.

METHODS AND ANALYSIS

Overview

This open-label, randomised controlled parallel group clinical trial will compare 26 weeks of hybrid closed-loop therapy versus 'standard therapy' for 120 adults (aged ≥25 years) with type 1 diabetes (protocol version 2.0, dated 29 March 2017). The standard therapy comparator consists of insulin delivered via either MDI or IPT, without real-time continuous glucose monitoring (RT-CGM), and was chosen to reflect current self-management of type 1 diabetes among adults in Australia.

The study is being conducted at seven university hospitals across Australia. The University of Melbourne is the coordinating academic institution, with St Vincent's Hospital Melbourne (Melbourne) the study sponsor and lead clinical site. Other clinical sites are: Flinders Medical Centre (Adelaide), Royal Hobart Hospital (Hobart), Royal Melbourne Hospital (Melbourne), Sir Charles Gairdner Hospital (Perth), The Alfred and Baker Heart and Diabetes Institute (Melbourne) and Westmead Hospital (Sydney). Other academic institutions involved are Sydney University and Deakin University. In parallel, a similar study of younger people (aged 12 to <25 years) with type 1 diabetes is being undertaken in Australia; the hybrid closed-loop system and primary outcome are aligned for the two studies.

Study outcomes

The study outcomes are listed in Table 1.

Table 1: Study outcomes

Primary outcome

The proportion of time sensor glucose is in target range (3.9–10.0 mmol/L) with hybrid closed-loop versus standard therapy (MDI or IPT without RT-CGM), measured by masked CGM at 23–26 weeks post-randomisation.

Secondary outcomes

Hybrid closed-loop therapy versus standard therapy (overall and for each of baseline MDI and IPT separately) for the measures listed below.

1. Glucose control:
   a. Masked CGM metrics for 24 h/day, day [06:00–00:00] and night [00:00–06:00] (measured at mid-study, end-of-study, and mid-study plus end-of-study combined):
      i. Proportion of time spent 3.9–10.0 mmol/L (excluding the primary outcome)
      ii. Proportion of time spent <2.8 mmol/L
      iii. Proportion of time spent <3.3 mmol/L
      iv. Proportion of time spent <3.9 mmol/L
      v. Proportion of time spent 3.9–7.8 mmol/L
      vi. Proportion of time spent >10.0 mmol/L
      vii. Proportion of time spent >13.9 mmol/L
      viii. Proportion of time spent >16.7 mmol/L
      ix. SD and coefficient of variation
      x. Mean glucose
   b. Fasting capillary blood glucose
   c. HbA_{1c}
   d. 1,5-anhydroglucitol
   e. Symptomatic hypoglycaemia (with blood glucose <3.5 mmol/L) requiring carbohydrate rescue (*n*)
2. Clinical:
   a. Change in total daily dose of insulin, and basal/bolus proportions
   b. Change in insulin-to-carbohydrate ratio
   c. Change in body weight
3. Psychosocial, sleep and cognitive functioning:
   a. Treatment satisfaction: The Diabetes Treatment Satisfaction Questionnaire (DTSQ) status and change versions
   b. Satisfaction with technology: Diabetes Management Experiences Questionnaire (DME-Q)
   c. Fear of hypoglycaemia: Hypoglycaemia Fear Survey short form (HFS-SF)
   d. Fear of hyperglycaemia: Hyperglycaemia Avoidance Scale (HAS)
   e. Hypoglycaemia Awareness: Gold Score
   f. Diabetes distress: Problem Areas in Diabetes (PAID)
   g. Diabetes-specific quality of life: DAWN Impact of Diabetes profile (DIDP)
   h. Diabetes-specific positive well-being: Well-being Questionnaire (W-BQ28) Positive Diabetes Well-being Subscale
   i. Cognitive function: Prospective and Retrospective Memory Questionnaire (PRMQ) and Psychomotor Vigilance Task (PVT-192)
   j. Driving: proportion of time-in-target glucose range while driving (Melbourne sites only)
   k. Sleep quality: Actigraph data, Pittsburgh Sleep Quality Index, Karolinska Sleepiness Scale

4. Electrocardiograph profile (via Holter monitor)
    a. Corrected QT interval (QT_c)
    b. Heart rate
    c. Cardiac arrhythmias
5. Human-technology interaction (participants using hybrid closed-loop system):
    a. Participant perceptions of the hybrid closed-loop system assessed via SMS data collection
    b. Participant expectations and experiences with the hybrid closed-loop system assessed via longitudinal semi-structured interviews (Melbourne sites only)
6. Health economic:
    a. Quality-adjusted life years calculated from the EQ-5D-5L
    b. Hypoglycaemic events and HbA_{1c}
    c. Participant and family reporting on work interruption
    d. Reported time spent on training, education and support, by the type of health professional resource used
    e. Diabetes management consumables (glucose strips, ketone strips, batteries, sensors, site dressings, lancets, needles, insulin)
    f. Resource utilisation tracked via linked administrative data from the Australian Medicare Benefits Schedule and Pharmaceutical Benefits Scheme
7. Biochemical markers of vascular disease risk:
    a. Cell adhesion molecules
    b. Oxidised low-density lipoprotein
    c. Myeloperoxidase
    d. MicroRNA signatures for arterial, renal and retinal complications
    e. Telomerase
    f. DNA methylation/acetylation
    g. Isoprostanes (blood and urine) and proteomics
    h. Clotting profile
8. Hybrid closed-loop system performance parameters:
    a. Proportion of time closed-loop active
    b. Unplanned exits from closed-loop (*n*)
    c. Sensor performance versus blood glucose meter as measured by MARD and sensor failures (*n*)
    d. Reported insulin delivery line failures (*n*)
    e. Participant calls to the technical help line (*n*)
9. Safety:
    a. Hospitalisations for diabetic ketoacidosis (*n*)
    b. Severe hypoglycaemia, defined as hypoglycaemia requiring the assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions (*n*)

The primary study outcome is the proportion of sensor glucose time-in-target range (3.9–10.0 mmol/L) with hybrid closed-loop versus standard therapy, measured by masked CGM 23–26 weeks post-randomisation. This primary end-point was selected to provide the best indication of individual participants' glucose control. The 3.9–10.0 mmol/L glucose range is aligned

with outcome metrics proposed by the JDRF Artificial Pancreas Project Consortium, is consistent with available data relating glucose control and complication prevention, and represents a realistic glucose target.[25 30]

CGM study outcome data will be collected by identical methods for participants in both groups. Hence, participants assigned hybrid closed-loop therapy will wear two identical glucose sensors for 2 weeks mid-study and 3 weeks at end-of-study—one sensor providing RT-CGM information to the user and directly linking to the hybrid closed-loop system, and a second sensor collecting masked CGM study outcome data. The closed-loop system performance parameters chosen as study outcome measures are based upon an international consensus report for outcomes measures in closed-loop trials.[30]

For closed-loop technology to achieve long-term clinical benefits, then in addition to positively impacting biomedical outcomes, user acceptance, uptake and adaptations are required.[31 32] Therefore, this study will assess aspects of psychosocial well-being via both subjective (questionnaires, interviews) and objective (actigraph, psychomotor task) methods. This holistic approach will progress understanding of the human factors involved, thereby enabling adaption of the technology in line with the person's expectations and experiences.[33] The study will also assess whether CGM has an impact on utilisation of health services and medications.

Eligibility

Inclusion and exclusion criteria for participation are listed in Table 2.

Table 2: Eligibility

Inclusion criteria
• Type 1 diabetes (as defined by the American Diabetes Association)[34] for at least 1 year
• Insulin regimen consisting of either:
o MDI with ≥4 injections per day (including ≥3 rapid-acting insulin injections and ≥1 long-acting insulin injection); or
o IPT established for ≥3 months
• Age 25–70 years inclusive
• HbA1c ≤10.5% (≤91 mmol/mol)
• Living in an area with internet and cellular phone coverage
• English speaking proficiency
Exclusion criteria
• Chronic kidney disease (eGFR <45 mL/min/1.73m^2)
• Current use of RT-CGM (defined as use >25% of the time during the past 3 months)
• Use of any non-insulin glucose-lowering agent within the past 3 months
• Oral or injected steroid use within the past 3 months
• Pregnancy, or pregnancy planned within study period
• Untreated coeliac disease or other malabsorption
• Uncontrolled thyroid disease
• Clinically-significant gastroparesis
• Uncontrolled hypertension (blood pressure: diastolic >100 or systolic >160 mmHg)
• History of myocardial infarction, severe uncontrolled heart failure, unstable angina, transient ischaemic attack, stroke, or thromboembolic disease in the past 3 months
• Poor visual acuity precluding use of the study technology
• Inability or unwillingness to meet protocol requirements
• Any severe or unstable medical or psychological condition which, in the opinion of the investigator, would compromise the ability to meet protocol requirements

The minimum inclusion age of 25 years was chosen to reflect a general adult population with type 1 diabetes while avoiding potential confounders associated with adolescence and emerging adulthood. This decision was informed by results of previous type 1 diabetes CGM and closed-loop studies, where individuals aged <25 years differed from those aged ≥25 years.[14 35]

Use of RT-CGM >25% of the time precludes inclusion. This decision was informed by study findings that adults aged ≥25 years with type 1 diabetes using RT-CGM with warning alarms had improved glucose control without increase in biochemical hypoglycaemia only when RT-CGM was worn ≥5–6 days/week.[35-37] When CGM is used less often or without warning alarms, evidence suggests no glucose control benefit.

Study diabetes management devices

Hybrid closed-loop system

The study hybrid closed-loop is the MiniMed™ 670G system, comprising a glucose sensor and transmitter coupled with an insulin pump containing a closed-loop algorithm (Medtronic, Northridge, CA, USA), and rapid-acting analogue insulin (either insulin aspart or insulin lispro) delivered subcutaneously. CGM data are transmitted to the pump every 5 minutes and the algorithm calculates the basal insulin dose (delivered at 5 min intervals) required to maintain the target glucose level. The algorithm uses a modified proportional integrative derivative model with insulin feedback based on an insulin delivery algorithm originally developed by Steil et al.[38] The algorithm also incorporates a supervisory model predictive component aiming to avoid insulin over-delivery.[39] For meals, the user estimates the amount of carbohydrate to be consumed (entering this into the pump) and checks their capillary blood glucose level. Using this information, an insulin bolus is calculated and delivered according to the individualised insulin-to-carbohydrate ratio and an insulin sensitivity factor determined by the algorithm (should a correction bolus be required).

The MiniMed™ 670G system has been deemed safe and effective for glucose control in a 3-month uncontrolled study [40 41] and an exercise study.[16] The system was approved for use by the US Food and Drug Administration in 2016.

Masked CGM

CGM data masked to both the participants and research team will be collected for study outcome measurements at three time-points: baseline pre-randomisation (3 weeks), mid-study (2 weeks) and end-of-study (3 weeks). For participants randomised to hybrid closed-loop, this masked CGM data collection will be in addition to the system's RT-CGM. The study uses Guardian™ Sensor 3 glucose sensors (Medtronic, Northridge, CA, USA). This sensor configuration has reported performance parameters of mean absolute relative difference (MARD) ± standard deviation (SD) of 9.6% ± 9.0% and mean functional sensor life of 146 ± 39 h when used with a Medtronic MiniMed™ 640G insulin pump.[42] By using a separate

device to collect CGM study outcome data, the device under investigation is not also being used to evaluate its own performance.

For masked CGM data collection, the glucose sensor will be inserted and the sensor recorder will be connected by the study team. During masked CGM, participants will be required to test capillary blood glucose levels at least 4 times per day with a CONTOUR® NEXT LINK meter (details below). Masked CGM data are collected retrospectively by uploading the recorder and the meter.

Blood glucose monitoring

All participants will be provided with a CONTOUR® NEXT LINK 2.4 blood glucose meter (Ascensia, Parsippany, NJ, USA) which is able to transmit data directly to the MiniMed™ 670G insulin pump. Pre-randomisation and for participants randomised to standard therapy, the CONTOUR® NEXT LINK 2.4 will be used in addition to their regular glucose meter during masked CGM. Use of the same glucose meter within the hybrid closed-loop system and for masked CGM calibration will standardise data collection.

Participants using MDI at enrolment will also be provided with an ACCU-CHEK® Aviva Expert blood glucose meter (Roche Diagnostics, Mannheim, Germany), selected for its in-built 'bolus calculator'. The bolus calculator uses the measured blood glucose level, calculated rapid-acting 'insulin on board', and the programmed insulin sensitivity factor and insulin-to-carbohydrate ratio to determine the recommended insulin bolus doses. The use of a meter with bolus calculator by those in the control group who continue with MDI will reflect the bolus calculators used by participants randomised to hybrid closed-loop therapy and by those using IPT randomised to standard diabetes therapy.

Diabetes management software

CareLink™, an internet-based platform from Medtronic, will be used for uploading insulin pump, glucose sensor and glucose meter data. The hybrid closed-loop system data are uploaded to a computer via the system's glucose meter USB connection; insulin pump, sensor and meter data are then accessible to study investigators.

Study design

This is a prospective, open-label, parallel design randomised controlled study involving 120 adults with type 1 diabetes (n=60 using MDI, n=60 using IPT). Study procedures will be undertaken by medical doctors with sub-speciality training in endocrinology, diabetes nurse educators, dieticians and research nurses. Throughout the study, the time taken for participant

education, training, clinical care and technical support will be recorded; the health professional time will be used in health economic analyses to determine implications for closed-loop becoming a mainstream therapy. Adherence to study protocols will be assessed at each study visit; verbal and written reminders of study instructions will be provided to improve protocol adherence. Participants will continue their usual diabetes clinical care with their treating clinicians during study participation. Participants will be randomised 1:1 either to hybrid closed-loop therapy or to continue using their current standard diabetes therapy (either MDI or IPT) for 26 weeks (Fig. 1). Use of RT-CGM will not be permitted during run-in or by participants randomised to standard diabetes therapy (though CGM without live alerts, e.g. Abbott FreeStyle® Libre, is permissible).

Sample size

The power calculation is for a parallel study design with two groups of equal size. It is based on SDs of the percentage time-in-target glucose range at 6 months (adjusted for baseline) observed for the subset of participants in two randomised clinical trials from the JDRF Study Group who had similar characteristics to participants being recruited here (Professor Roy Beck, personal communication). The SD (95% confidence interval) for pump users was 9% (8%, 12%) and for MDI users was 10% (7%, 19%).

From an initial overall sample size of n=120, with a dropout rate of 10%, a common SD of 9% and a type I error rate of 5%, the power to detect a minimum absolute difference of 5% time-in-target glucose range would be 80%. A more conservative scenario with a dropout rate of 20%, and unequal SDs of 12% and 19% for pump and MDI users, respectively, increases the minimum detectable absolute difference to 9% with power of 80%.

Study schedule

The study will consist of 16 visits including the run-in and intervention periods. Key activities undertaken during each visit are shown in Table 3. Participants will be provided with 24-hour telephone contacts for support if required. Health professionals will log all time taken training and communicating with the study participants.

Table 3: Study visits

Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Weeks from randomisation			-3	-2	-1	0	1	~7	11	12	13	23	24	25	26	26	39
Clinical assessment	X					X					X					X	
Time with health professional		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HbA_{1c}	X					X					X					X	
β-hCG, C-peptide	X																
CHO-counting education		X									X						
Insulin pump training							X										
Insulin dose review		X						X			X					X	
Logbook provision			X														
Logbook data collection				X	X	X	X	X	X	X	X	X	X	X	X	X	
Masked CGM insertion			X	X	X				X	X		X	X	X			
Glucose meter upload				X	X	X	X	X	X	X	X	X	X	X	X	X	
Psychosocial, sleep, cognitive functioning surveys	X										X					X	
Cognitive performance device provision			X						X			X					
Actigraphy & sleep diary provision			X	X	X				X	X		X	X	X			
Semi-structured interviews							X		X							X	X
Driving device and diary provision			X	X	X				X	X		X	X	X			
Holter monitor provision			X						X			X					
Vascular disease risk markers						X										X	

Run-in period

After enrolment, there will be a run-in period lasting at least 5 weeks. Participants will undergo initial medical, psychosocial and cognitive assessments. Their diabetes-related knowledge and carbohydrate-counting proficiency will be assessed and their insulin dosing

will be optimised. Participants will be provided with detailed training and support to use the study glucose meters and masked CGM devices. Education will be provided by diabetes nurse educators and dieticians to optimise participants' diabetes self-management including carbohydrate-counting. The optimisation of carbohydrate-counting is central to baseline optimisation for all participants in the study—this aims to achieve the best possible match of bolus insulin doses to the individuals' requirements for the carbohydrate consumed for both groups, thereby testing the closed-loop aspect of the hybrid closed-loop system's insulin delivery in comparison with standard therapy.

After provision of education, data will be collected for 3 weeks of baseline masked CGM, actigraphy (sleep data) and from the self-reported diabetes logbook. Driving log data (to associate with the CGM data) will also be collected during these 3 weeks for participants at the three clinical sites in Melbourne. At the end of the run-in period, the CGM data will be uploaded and checked to ensure data are available for at least 70% of the time.[35] If the minimum required CGM data are not available, an additional week of CGM will be undertaken to fulfil the protocol requirements. At the end of the run-in, baseline blood and urine samples will be collected for measurement of HbA_{1c} and biochemical markers of vascular disease risk.

Randomisation

Eligible participants will be randomised after completing the run-in. Group allocation will be a 1:1 ratio using minimisation with three variables, all of which are expected to be highly prognostic of the primary outcome. These minimisation variables are: i) the proportion of time-in-target glucose range at baseline (dichotomised to ≤50% and >50%); ii) study centre (seven clinical sites); and iii) insulin delivery modality (MDI or IPT). Randomisation will be performed by an independent group of statisticians using central randomisation software, and will be implemented into an electronic participant record system.

The nature of the study groups does not allow blinding of participants or investigators.

Intervention period

After randomisation, there will be a 26-week intervention period.

Participants randomised to standard therapy will continue using their current insulin delivery modality (MDI or IPT) and will be instructed to refrain from using RT-CGM during the study.

Participants randomised to hybrid closed-loop therapy will receive general insulin pump and CGM education and training, plus instruction regarding usage of the study hybrid closed-loop system. This education and training period may take up to 4 weeks (likely longer for those using MDI than IPT at baseline). The hybrid closed-loop system will be programmed with participants' usual insulin-to-carbohydrate ratios and insulin sensitivity factors, as well as their usual basal rates (or the basal rates determined by their clinicians for those participants transitioning from MDI). Participants will be provided with a 24-hour technical help telephone contact for the hybrid closed-loop system.

Participants at the three clinical sites in Melbourne who are randomised to hybrid closed-loop therapy will undergo four semi-structured interviews to assess their expectations of, and experiences with, the technology. These interviews will be conducted at randomisation, then at 11 weeks, 26 weeks and 39 weeks post-randomisation.

Participants will have mid-study data collected between 11 weeks to 13 weeks post-randomisation. Two weeks of masked CGM data, cognitive assessments and actigraphy will be collected, plus driving data for participants at the Melbourne sites. Clinical review with assessment of diabetes management and carbohydrate-counting, and adjustment of therapy and further education as required, will be undertaken 13 weeks post-randomisation. At this visit, psychosocial questionnaires will be completed and venous samples for HbA_{1c} will be collected.

Participants will have end-of-study data collected between 23 to 26 weeks post-randomisation. Three weeks of masked CGM data, cognitive assessments and actigraphy will be collected, plus driving data for participants at the Melbourne sites. At the end of the three-week period, the CGM data will be uploaded and checked for available data at least 70% of the time. If 70% of CGM data are not available, an additional week of CGM data will be collected. At the end-of-study visit (26 weeks post-randomisation), psychosocial questionnaires will be completed, and venous and urine samples will be collected for HbA_{1c} and biochemical markers of vascular disease risk. Participants in the hybrid closed-loop group will change back to using their usual insulin delivery modality (MDI or IPT). Doctor visit data from the Medicare Benefits Schedule and insulin prescription data from the Pharmaceutical Benefits Scheme will be accessed for study participants.

Statistical methods

The primary analysis will assess differences in the proportion of time-in-target glucose sensor range (3.9–10.0 mmol/L) with hybrid closed-loop versus standard therapy, measured by masked CGM at 23–26 weeks post-randomisation on an intention-to-treat basis using analysis of covariance (ANCOVA) with adjustment for baseline time-in-target range. A *p*-value threshold of <0.05 will be used to determine statistical significance.

Model fit will be evaluated by exploration of residuals. If the model is of poor fit, the outcome variable will be transformed and the model refitted and evaluated. If unsuccessful, nonparametric analysis will be performed.

Analysis of continuous secondary outcomes will also use ANCOVA with adjustment for baseline time-in-target range, whereas Poisson or negative binomial regression will be used for count outcomes and logistic regression will be used for binary outcomes. Subgroup analysis by baseline insulin delivery modality will be performed by inclusion of an interaction term in the regression modelling or by a stratified analysis when non-parametric methods are used.

No adjustment for multiplicity is planned. All results for primary and secondary outcomes will be reported.[43] No interim analysis is planned.

Health economic evaluation

An economic evaluation will determine the incremental cost of home-based hybrid closed-loop versus standard diabetes therapy in Australia. This analysis will quantify costs directly associated with hybrid closed-loop and standard diabetes therapy plus other impacts on the health system (Table 1). Outcomes will be assessed in quality-adjusted life years for changes in health-related quality of life, and for the likely long-term impact of changes in glucose control on long-term outcomes using a type 1 diabetes simulation model.

Safety assessments

Safety parameters to be assessed include severe hypoglycaemia, ketoacidosis, and unplanned hospitalisations directly related to the study (Table 1).

Efficacy assessments

Efficacy parameters to be assessed include glucose control, clinical measures, psychosocial and cognitive functioning, human-technology interaction, health economic measures and biochemical markers of vascular disease risk (Table 1).

Closed-loop system performance parameters

Closed-loop system performance parameters to be assessed relate to the system overall, to individual system components and to system usability (Table 1).

Trial oversight

The study will be conducted in accordance with the principles of the Declaration of Helsinki and guidelines for Good Clinical Practice (GCP).

The day-to-day study management will be the responsibility of the investigators at each clinical site. The Principal Investigator and study project manager will maintain regular correspondence with all investigators and study coordinators. The Principal Investigator, with the sites' lead investigators, will assume responsibility for the progress of the study in accordance with agreed timelines and milestones with the study funders. A combined data safety and monitoring board (DSMB) will be established for this study and the aligned study, independent from the study investigators, comprising adult and paediatric physicians experienced in statistics and clinical trials. The study project manager will liaise with the study teams in all centres to establish procedures and ensure that the study is carried out according to the protocol and to standards of GCP, with robust systems for reporting adverse events. The study project manager will be responsible for the central preparations of data for presentation to the DSMB.

ETHICS AND DISSEMINATION

The study has received ethics approval from the lead site Human Research Ethics Committee. Other clinical sites provide oversight through local governance committees. Any substantial amendments to the study protocol will be reported to the lead site ethics committee for approval prior to implementation, and updated on the trial registry, with the study investigators being advised in writing.

All potential participants will be provided with written and verbal information regarding the study, the procedures involved and all potential risks related to participating. A study investigator will obtain written informed consent from each participant prior to commencing study procedures. All personal information about potential and enrolled participants will be de-identified to protect confidentiality before, during and after the trial. Standard operating procedures for reporting all adverse events, device-related adverse events and severe adverse events will be in place. The Human Research Ethics Committees and the Therapeutic Goods

Administration of Australia will be informed of any serious adverse events and any unexpected device-related adverse events.

Screening and recruitment commenced in May 2017. It is anticipated that the study visits will be completed by May 2019. The results of the study will be disseminated at national and international conferences and by peer-reviewed publications.

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Contributors

SAM, MIDB, PGC, AJJ, ACK, JS, GMW, TWJ and DNO designed the study. SAM and DNO drafted the manuscript. All authors contributed to the writing and/or critical review of the study protocol and reviewed this manuscript for intellectual content. DNO is the principal investigator and guarantor.

The Australian JDRF Closed-Loop Research Group members have had input into the protocol, and are named as follows: Mary B Abraham, Geoffrey R Ambler, Leon A Bach, Morton G Burt, Fergus J Cameron, Philip M Clarke, Neale D Cohen, Peter G Colman, Elizabeth A Davis, Martin I de Bock, Jan M Fairchild, Elizabeth A Geelhoed, Christel Hendrieckx, D Jane Holmes-Walker, Jodie C Horsburgh, Alicia J Jenkins, Timothy W Jones, Joey Kaye, Anthony C Keech, Bruce R King, Kavita Kumareswaran, Melissa H Lee, Richard J MacIsaac, Sybil A McAuley, Roland W McCallum, Jennifer A Nicholas, David N O'Neal, Barbora Paldus, Catriona Sims, Grant J Smith, Jane Speight, Stephen N Stranks, Vijaya Sundararajan, Steven Trawley, Sara Vogrin and Glenn M Ward.

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The study funders and sponsor did not have any role in study design or contribution to this manuscript, and they will not be involved in collection, management, analysis or interpretation of the data. The study funders will not have any role in writing the study report or the decision to submit the report for publication.

Competing interests

MIDB and NDC report receiving speaker honoraria from Medtronic. DJH reports receiving speaker and advisory board honoraria from Medtronic. RWM reports receiving conference travel and accommodation support from Medtronic. JS reports that the ACBRD has received honoraria from Medtronic in relation to her speaking engagements and role in advisory boards. DNO reports receiving speaker honoraria and research grants from Medtronic.

Ethics approval

St Vincent's Hospital Melbourne Human Research Ethics Committee (lead site, approval number HREC-D 088/16).

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FIGURE LEGEND

Figure 1: Study protocol overview

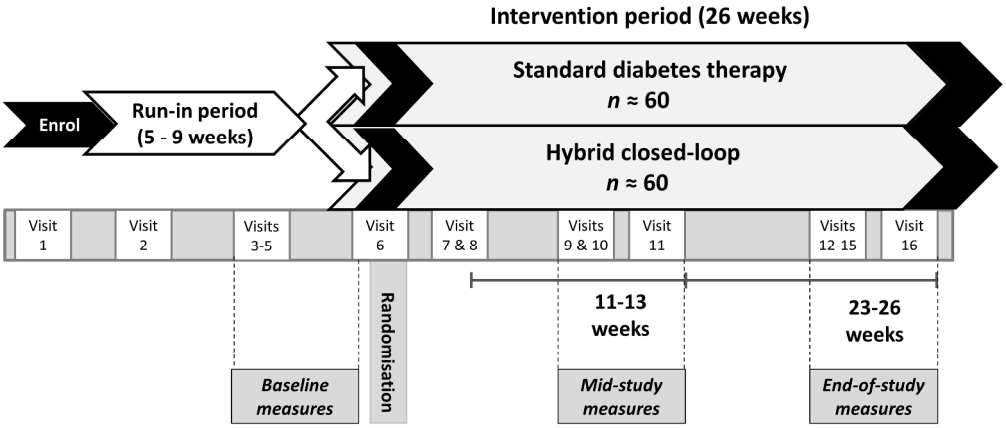

Figure 1: Study protocol overview

254x190mm (300 x 300 DPI)

BMJ Open

Efficacy of 6 months hybrid closed-loop insulin delivery on glucose control, psychosocial well-being, sleep and cognition in adults with type 1 diabetes: a randomised controlled trial protocol

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Efficacy of 6 months hybrid closed-loop insulin delivery on glucose control, psychosocial well-being, sleep and cognition in adults with type 1 diabetes: a randomised controlled trial protocol

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ABSTRACT

Introduction

Manual determination of insulin dosing largely fails to optimise glucose control in type 1 diabetes. Automated insulin delivery via closed-loop systems has improved glucose control in short-term studies. Longer-term home-based studies of closed-loop system effects on glucose, psychosocial well-being, sleep and cognition are merited.

Methods and analysis

This open-label, seven-centre, randomised controlled parallel group clinical trial will compare home-based hybrid closed-loop versus standard diabetes therapy in Australia. Adults aged ≥25 years with type 1 diabetes using intensive insulin therapy (via multiple daily injections or insulin pump, total enrolment target *n*=120) will undertake a run-in period including diabetes and carbohydrate-counting education, clinical optimisation and baseline data collection. Participants will then be randomised 1:1 either to 26 weeks of MiniMed™ 670G hybrid closed-loop system therapy (Medtronic, Northridge, CA, USA) or continuation of their current diabetes therapy. The hybrid closed-loop system delivers insulin automatically to address basal requirements and correct to target glucose level, while bolus doses for meals require user initiation and carbohydrate estimation. Analysis will be intention-to-treat, with the primary outcome time in continuous glucose monitoring (CGM) target range (3.9–10.0 mmol/L) during the final 3 weeks of intervention. Secondary outcomes include: other CGM parameters, HbA_{1c}, severe hypoglycaemia, psychosocial well-being, sleep, cognition, electrocardiography, costs, quality of life, biomarkers of vascular health and hybrid closed-loop system performance. Semi-structured interviews will assess the expectations and experiences of a sub-group of hybrid closed-loop users.

Ethics and dissemination

The study has Human Research Ethics Committee approval. The study will be conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Results will be disseminated at scientific conferences and via peer-reviewed publications.

Trial registration number

ACTRN12617000520336, pre-results

Strengths and limitations of the study

- Multi-centre, randomised controlled parallel group trial of 26 weeks home-based hybrid closed-loop versus standard therapy
- Broad outcomes will be assessed in addition to glucose control: psychosocial, sleep, cognition, electrocardiography, vascular health biomarkers and health economic measures
- The standard therapy comparator—multiple daily insulin injections or insulin pump therapy, without real-time continuous glucose monitoring—reflects current practice in Australia for most adults with type 1 diabetes, though this may not reflect standard care in other countries
- The study emphasises education and clinical optimisation for all participants pre-randomisation, and the visit schedule is identical for both groups (by design, continuous glucose monitoring information is only available to the closed-loop group)
- This study of adults aged ≥25 years has glucose end-points aligned with a concurrent study examining hybrid closed-loop for young people aged 12 to <25 years, thereby facilitating comparison of metabolic outcomes between the two populations

INTRODUCTION

Advances in type 1 diabetes insulin regimens and glucose monitoring have occurred over recent decades, facilitating improved glucose control and resulting in better health and quality of life.[1-4] The long-term vascular complications of type 1 diabetes are reduced by intensive insulin therapy compared with less intensive therapy.[1 2] Consequently, intensive insulin therapy—with subcutaneous administration via either multiple daily injections (MDI) or insulin pump therapy (IPT)—is a core strategy in current type 1 diabetes management.[5] Nevertheless, even with modern therapies, only 20–30% of adults with type 1 diabetes achieve HbA_{1c} targets[6 7], and long-term vascular complications and reduced life expectancy continue to be a reality for people with type 1 diabetes.[8 9]

Insulin requirements can vary unpredictably. They are impacted by time of day, meals, exercise, illness and antecedent hypoglycaemia. Manual determination of insulin dosing by people with type 1 diabetes requires continuous vigilance to maintain glucose levels within a healthy range. Insulin dosing decisions carry cognitive and emotional burden, and may be inconsistent due to fatigue, distress, fluctuating glucose levels or coexistent fear of hypoglycaemia. Hence, manual determination of insulin dosing represents an imperfect strategy to optimise glucose control. Further advances in technology are required to improve the match of insulin delivered to individuals' varying insulin requirements, and to minimise the burden of type 1 diabetes.

Closed-loop systems are designed to maintain glucose levels at a predetermined target by linking continuous glucose monitoring (CGM) information with an insulin dosing algorithm for automated subcutaneous insulin delivery by a pump.[10] These systems are being developed to address the need for improving glucose control while reducing the burden associated with treatment regimens. There is increasing scientific literature of randomised controlled studies reporting improved glucose control with short-term use of closed-loop systems (up to 3 months) compared with conventional insulin pumps.[11-15] A recent meta-analysis of outpatient randomised controlled trials with intervention periods ranging from 4 days to 12 weeks reported that single-hormone (insulin alone) closed-loop systems improve time-in-target glucose range and reduce time spent in hypoglycaemia compared with conventional IPT (with/without CGM).[16] Overall, time-in-target glucose range had a mean (95% confidence interval) absolute increase of 11.1% (6.9, 15.2), and the time spent in hypoglycaemia had an absolute reduction of 1.9% (0.4, 3.4). Studies in this meta-analysis used 'hybrid closed-loop' systems with automated insulin delivery to address basal requirements and correct to target

glucose, and user-initiated bolus insulin to address carbohydrate consumption. Results from a short-term randomised crossover study challenging a closed-loop system with both moderate- and high-intensity exercise indicated that closed-loop glucose control was safe; only a single episode of mild hypoglycaemia occurred and marked hyperglycaemic excursions were limited.[17] In an uncontrolled study, there were no safety concerns when 14 participants used free-living closed-loop 24/7 for 6 months.[18]

For individuals with type 1 diabetes, both hypoglycaemia and hyperglycaemia can affect physical and emotional well-being, quality of life, and activities of daily living such as driving.[4 19-21] Moreover, type 1 diabetes places significant burden on caregivers, families, workplaces and health services.[22-24] Closed-loop technology has shown promise to address the limitations of current therapy in relation to these burdens.[25] Qualitative and small-scale quantitative sub-studies in closed-loop trials have shown user acceptability and treatment satisfaction are high with closed-loop systems in home settings, particularly for overnight use when there is minimal manual interaction for meals and activity.[26-28] Although intrusive device alerts, device size and technical difficulties can negatively affect the overall experience, users typically report benefits outweighing annoyances, which they anticipate will be overcome with future iterations of the technology.[27-29] However, the only published randomised closed-loop trial involving adults to have included established, validated psychological measures, reported no between-group differences in treatment satisfaction or fear of hypoglycaemia.[30]

HbA_{1c}, a measurement of average glycaemia during the preceding 10–12 weeks, predicts the risk of developing long-term complications and is valuable for assessing glycaemic trends in populations over time.[1 2 31] However, HbA_{1c} cannot provide information about glucose variability or time-in-target glucose range, and is even considered an unreliable indicator of an individual's mean glucose.[32] A recent large longitudinal registry study reported lower cardiovascular and all-cause mortality in individuals using IPT compared with MDI, even without between-group differences in HbA_{1c}.[33] The mortality difference observed may have been attributable to factors such as time-in-target glucose range or glucose variability (not reflected in HbA_{1c}). Consequently, HbA_{1c} may be of limited value in comparison with CGM when assessing an individual's glucose levels in response to automated closed-loop insulin delivery.

With short-term randomised controlled studies of closed-loop systems (conducted in camp/hotel and home settings) demonstrating improvements in glucose control,[16] it remains

to be determined whether these findings are sustained in the longer term in the home setting and whether diabetes-related vascular complications may be influenced. Longer-term randomised controlled home-based studies—with closed-loop implemented day and night—are required. In addition, the impact of closed-loop insulin delivery on patient-reported outcomes such as fear of hypoglycaemia, treatment satisfaction, sleep quality and cognition remains a significant gap in the evidence base.[34] Finally, the benefits associated with this new technology need to be balanced against its cost.

In Australia, the government presently subsidises the purchase of insulin, injection needles, blood glucose monitoring strips and insulin pump delivery consumables for people with type 1 diabetes.[35] Insulin pumps are not government-subsidised, but are available via either direct purchase or in conjunction with a private health insurance fund. CGM is government-subsidised only for eligible individuals under 21 years of age.[36] As a result, only a small fraction of adults with type 1 diabetes use CGM on a regular basis. Hence, standard diabetes therapy for adults in Australia currently involves subcutaneous intensive insulin therapy delivered via either MDI or pump, together with finger-prick blood glucose monitoring.

We hypothesise that hybrid closed-loop insulin delivery compared with manual insulin dosing will improve glucose control and non-glucose outcomes for adults with type 1 diabetes. The overall aim of the study is to evaluate the efficacy of 6 months of hybrid closed-loop insulin delivery on glucose control, psychosocial well-being, sleep quality, cognition and markers of vascular disease risk compared with standard diabetes therapy for adults with type 1 diabetes.

METHODS AND ANALYSIS

Overview

This open-label, randomised controlled parallel group clinical trial will compare 26 weeks of hybrid closed-loop therapy versus 'standard therapy' for 120 adults (aged ≥25 years) with type 1 diabetes (protocol version 2.0, dated 29 March 2017). The standard therapy comparator consists of insulin delivered via either MDI or IPT, without real-time continuous glucose monitoring (RT-CGM), and was chosen to reflect current self-management of type 1 diabetes among adults in Australia.

The study is being conducted at seven university hospitals across Australia. The University of Melbourne is the coordinating academic institution, with St Vincent's Hospital Melbourne (Melbourne) the study sponsor and lead clinical site. Other clinical sites are: Flinders Medical

Centre (Adelaide), Royal Hobart Hospital (Hobart), Royal Melbourne Hospital (Melbourne), Sir Charles Gairdner Hospital (Perth), The Alfred and Baker Heart and Diabetes Institute (Melbourne) and Westmead Hospital (Sydney). Other academic institutions involved are Sydney University and Deakin University. In parallel, a similar study of younger people (aged 12 to <25 years) with type 1 diabetes is being undertaken in Australia; the hybrid closed-loop system and primary outcome are aligned for the two studies.

Study outcomes

The study outcomes are listed in Table 1.

Table 1: Study outcomes

Primary outcome

The proportion of time sensor glucose is in target range (3.9–10.0 mmol/L) with hybrid closed-loop versus standard therapy (MDI or IPT without RT-CGM), measured by masked CGM at 23–26 weeks post-randomisation.

Secondary outcomes

Hybrid closed-loop therapy versus standard therapy (overall and for each of baseline MDI and IPT separately) for the measures listed below.

1. Glucose control:
   a. Masked CGM metrics for 24 h/day, day [06:00–00:00] and night [00:00–06:00] (measured at mid-study, end-of-study, and mid-study plus end-of-study combined):
      i. Proportion of time spent 3.9–10.0 mmol/L (excluding the primary outcome)
      ii. Proportion of time spent <2.8 mmol/L
      iii. Proportion of time spent <3.3 mmol/L
      iv. Proportion of time spent <3.9 mmol/L
      v. Proportion of time spent 3.9–7.8 mmol/L
      vi. Proportion of time spent >10.0 mmol/L
      vii. Proportion of time spent >13.9 mmol/L
      viii. Proportion of time spent >16.7 mmol/L
      ix. SD and coefficient of variation
      x. Mean glucose
   b. Fasting capillary blood glucose
   c. HbA_{1c}
   d. 1,5-anhydroglucitol
   e. Symptomatic hypoglycaemia (with blood glucose <3.5 mmol/L) requiring carbohydrate rescue (*n*)
2. Clinical:
   a. Change in total daily dose of insulin, and basal/bolus proportions
   b. Change in insulin-to-carbohydrate ratio
   c. Change in body weight
3. Psychosocial, sleep and cognitive functioning:
   a. Treatment satisfaction: The Diabetes Treatment Satisfaction Questionnaire (DTSQ) status

and change versions
   b. Satisfaction with technology: Diabetes Management Experiences Questionnaire (DME-Q)
   c. Fear of hypoglycaemia: Hypoglycaemia Fear Survey short form (HFS-SF)
   d. Fear of hyperglycaemia: Hyperglycaemia Avoidance Scale (HAS)
   e. Hypoglycaemia Awareness: Gold Score
   f. Diabetes distress: Problem Areas in Diabetes (PAID)
   g. Diabetes-specific quality of life: DAWN Impact of Diabetes profile (DIDP)
   h. Diabetes-specific positive well-being: Well-being Questionnaire (W-BQ28) Positive Diabetes Well-being Subscale
   i. Cognitive function: Prospective and Retrospective Memory Questionnaire (PRMQ) and Psychomotor Vigilance Task (PVT-192)
   j. Driving: proportion of time-in-target glucose range while driving (Melbourne sites only)
   k. Sleep quality: Actigraph data, Pittsburgh Sleep Quality Index, Karolinska Sleepiness Scale
4. Electrocardiograph profile (via Holter monitor)
   a. Corrected QT interval (QT_c)
   b. Heart rate
   c. Cardiac arrhythmias
5. Human-technology interaction (participants using hybrid closed-loop system):
   a. Participant perceptions of the hybrid closed-loop system assessed via SMS data collection
   b. Participant expectations and experiences with the hybrid closed-loop system assessed via longitudinal semi-structured interviews (Melbourne sites only)
6. Health economic:
   a. Quality-adjusted life years calculated from the EQ-5D-5L
   b. Hypoglycaemic events and HbA_{1c}
   c. Participant and family reporting on work interruption
   d. Reported time spent on training, education and support, by the type of health professional resource used
   e. Diabetes management consumables (glucose strips, ketone strips, batteries, sensors, site dressings, lancets, needles, insulin)
   f. Resource utilisation tracked via linked administrative data from the Australian Medicare Benefits Schedule and Pharmaceutical Benefits Scheme
7. Biochemical markers of vascular disease risk:
   a. Cell adhesion molecules
   b. Oxidised low-density lipoprotein
   c. Myeloperoxidase
   d. MicroRNA signatures for arterial, renal and retinal complications
   e. Telomerase
   f. DNA methylation/acetylation
   g. Isoprostanes (blood and urine) and proteomics
   h. Clotting profile
8. Hybrid closed-loop system performance parameters:
   a. Proportion of time closed-loop active
   b. Unplanned exits from closed-loop (*n*)
   c. Sensor performance versus blood glucose meter as measured by MARD and sensor failures (*n*)
   d. Reported insulin delivery line failures (*n*)
   e. Participant calls to the technical help line (*n*)

9. Safety:
   a. Hospitalisations for diabetic ketoacidosis (*n*)
   b. Severe hypoglycaemia, defined as hypoglycaemia requiring the assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions (*n*)

The primary study outcome is the proportion of sensor glucose time-in-target range (3.9–10.0 mmol/L) with hybrid closed-loop versus standard therapy, measured by masked CGM 23–26 weeks post-randomisation. This primary end-point was selected to provide the best indication of individual participants' glucose control. The 3.9–10.0 mmol/L glucose range is aligned with outcome metrics proposed by the JDRF Artificial Pancreas Project Consortium, is consistent with available data relating glucose control and complication prevention, and represents a realistic glucose target.[32 37]

CGM study outcome data will be collected by identical methods for participants in both groups. Hence, participants assigned hybrid closed-loop therapy will wear two identical glucose sensors for 2 weeks mid-study and 3 weeks at end-of-study—one sensor providing RT-CGM information to the user and directly linking to the hybrid closed-loop system, and a second sensor collecting masked CGM study outcome data. The closed-loop system performance parameters chosen as study outcome measures are based upon an international consensus report for outcomes measures in closed-loop trials.[37]

For closed-loop technology to achieve long-term clinical benefits, then in addition to positively impacting biomedical outcomes, user acceptance, uptake and adaptations are required.[28 38] Therefore, this study will assess aspects of psychosocial well-being via both subjective (questionnaires, interviews) and objective (actigraph, psychomotor task) methods. This holistic approach will progress understanding of the human factors involved, thereby enabling adaption of the technology in line with the person's expectations and experiences.[39] The study will also assess whether CGM has an impact on utilisation of health services and medications.

Eligibility

Inclusion and exclusion criteria for participation are listed in Table 2.

Table 2: Eligibility

Inclusion criteria
• Type 1 diabetes (as defined by the American Diabetes Association)[40] for at least 1 year
• Insulin regimen consisting of either:
o MDI with ≥4 injections per day (including ≥3 rapid-acting insulin injections and ≥1 long-acting insulin injection); or
o IPT established for ≥3 months
• Age 25–70 years inclusive
• HbA1c ≤10.5% (≤91 mmol/mol)
• Living in an area with internet and cellular phone coverage
• English speaking proficiency
Exclusion criteria
• Chronic kidney disease (eGFR <45 mL/min/1.73m^2)
• Current use of RT-CGM (defined as use >25% of the time during the past 3 months)
• Use of any non-insulin glucose-lowering agent within the past 3 months
• Oral or injected steroid use within the past 3 months
• Pregnancy, or pregnancy planned within study period
• Untreated coeliac disease or other malabsorption
• Uncontrolled thyroid disease
• Clinically-significant gastroparesis
• Uncontrolled hypertension (blood pressure: diastolic >100 or systolic >160 mmHg)
• History of myocardial infarction, severe uncontrolled heart failure, unstable angina, transient ischaemic attack, stroke, or thromboembolic disease in the past 3 months
• Poor visual acuity precluding use of the study technology
• Inability or unwillingness to meet protocol requirements
• Any severe or unstable medical or psychological condition which, in the opinion of the investigator, would compromise the ability to meet protocol requirements

The minimum inclusion age of 25 years was chosen to reflect a general adult population with type 1 diabetes while avoiding potential confounders associated with adolescence and emerging adulthood. This decision was informed by results of previous type 1 diabetes CGM and closed-loop studies, where individuals aged <25 years differed from those aged ≥25 years.[14 41]

Use of RT-CGM >25% of the time precludes inclusion. This decision was informed by study findings that adults aged ≥25 years with type 1 diabetes using RT-CGM with warning alarms had improved glucose control without increase in biochemical hypoglycaemia only when RT-CGM was worn ≥5–6 days/week.[41-43] When CGM is used less often or without warning alarms, evidence suggests no glucose control benefit.

Study diabetes management devices

Hybrid closed-loop system

The study hybrid closed-loop is the MiniMed™ 670G system, comprising a glucose sensor and transmitter coupled with an insulin pump containing a closed-loop algorithm (Medtronic, Northridge, CA, USA), and rapid-acting analogue insulin (either insulin aspart or insulin lispro) delivered subcutaneously. CGM data are transmitted to the pump every 5 minutes and the algorithm calculates the basal insulin dose (delivered at 5 min intervals) required to maintain the target glucose level. The algorithm uses a modified proportional integrative derivative model with insulin feedback based on an insulin delivery algorithm originally developed by Steil et al.[44] The algorithm also incorporates a supervisory model predictive component aiming to avoid insulin over-delivery.[45] For meals, the user estimates the amount of carbohydrate to be consumed (entering this into the pump) and checks their capillary blood glucose level. Using this information, an insulin bolus is calculated and delivered according to the individualised insulin-to-carbohydrate ratio and an insulin sensitivity factor determined by the algorithm (should a correction bolus be required).

The MiniMed™ 670G system has been deemed safe and effective for glucose control in a 3-month uncontrolled study [46 47] and an exercise study.[17] The system was approved for use by the US Food and Drug Administration in 2016.

Masked CGM

CGM data masked to both the participants and research team will be collected for study outcome measurements at three time-points: baseline pre-randomisation (3 weeks), mid-study (2 weeks) and end-of-study (3 weeks). For participants randomised to hybrid closed-loop, this masked CGM data collection will be in addition to the system's RT-CGM. The study uses Guardian™ Sensor 3 glucose sensors (Medtronic, Northridge, CA, USA). This sensor configuration has reported performance parameters of mean absolute relative difference (MARD) ± standard deviation (SD) of 9.6% ± 9.0% and mean functional sensor life of 146 ± 39 h when used with a Medtronic MiniMed™ 640G insulin pump.[48] By using a separate

device to collect CGM study outcome data, the device under investigation is not also being used to evaluate its own performance.

For masked CGM data collection, the glucose sensor will be inserted and the sensor recorder will be connected by the study team. During masked CGM, participants will be required to test capillary blood glucose levels at least 4 times per day with a CONTOUR® NEXT LINK meter (details below). Masked CGM data are collected retrospectively by uploading the recorder and the meter.

Blood glucose monitoring

All participants will be provided with a CONTOUR® NEXT LINK 2.4 blood glucose meter (Ascensia, Parsippany, NJ, USA) which is able to transmit data directly to the MiniMed™ 670G insulin pump. Pre-randomisation and for participants randomised to standard therapy, the CONTOUR® NEXT LINK 2.4 will be used in addition to their regular glucose meter during masked CGM. Use of the same glucose meter within the hybrid closed-loop system and for masked CGM calibration will standardise data collection.

Participants using MDI at enrolment will also be provided with an ACCU-CHEK® Aviva Expert blood glucose meter (Roche Diagnostics, Mannheim, Germany), selected for its in-built 'bolus calculator'. The bolus calculator uses the measured blood glucose level, calculated rapid-acting 'insulin on board', and the programmed insulin sensitivity factor and insulin-to-carbohydrate ratio to determine the recommended insulin bolus doses. The use of a meter with bolus calculator by those in the control group who continue with MDI will reflect the bolus calculators used by participants randomised to hybrid closed-loop therapy and by those using IPT randomised to standard diabetes therapy.

Diabetes management software

CareLink™, an internet-based platform from Medtronic, will be used for uploading insulin pump, glucose sensor and glucose meter data. The hybrid closed-loop system data are uploaded to a computer via the system's glucose meter USB connection; insulin pump, sensor and meter data are then accessible to study investigators.

Study design

This is a prospective, open-label, parallel design randomised controlled study involving adults with type 1 diabetes (overall target n=120, with ≥40% using MDI and ≥40% using IPT). Study procedures will be undertaken by medical doctors with sub-speciality training in endocrinology, diabetes nurse educators, dieticians and research nurses. Throughout the

study, the time taken for participant education, training, clinical care and technical support will be recorded; the health professional time will be used in health economic analyses to determine implications for closed-loop becoming a mainstream therapy. Adherence to study protocols will be assessed at each study visit; verbal and written reminders of study instructions will be provided to improve protocol adherence. Participants will continue their usual diabetes clinical care with their treating clinicians during study participation. Participants will be randomised 1:1 either to hybrid closed-loop therapy or to continue using their current standard diabetes therapy (either MDI or IPT) for 26 weeks (Fig. 1). Use of RT-CGM will not be permitted during run-in or by participants randomised to standard diabetes therapy (though CGM without live alerts, e.g. Abbott FreeStyle® Libre, is permissible).

Patient involvement

Investigator discussions with patients throughout provision of clinical care and during previous research studies were taken into consideration when designing this study protocol. The burden of the study intervention will be assessed via SMS data collection and during semi-structured interviews (see Table 1, sections 5a and 5b).

Sample size

The power calculation is for a parallel study design with two groups of equal size. It is based on SDs of the percentage time-in-target glucose range at 6 months (adjusted for baseline) observed for the subset of participants in two randomised clinical trials from the JDRF Study Group who had similar characteristics to participants being recruited here (Professor Roy Beck, personal communication). The SD (95% confidence interval) for pump users was 9% (8%, 12%) and for MDI users was 10% (7%, 19%).

From an initial overall sample size of n=120, with a dropout rate of 10%, a common SD of 9% and a type I error rate of 5%, the power to detect a minimum absolute difference of 5% time-in-target glucose range would be 80%. A more conservative scenario with a dropout rate of 20%, and unequal SDs of 12% and 19% for pump and MDI users, respectively, increases the minimum detectable absolute difference to 9% with power of 80%.

Study schedule

The study will consist of 16 visits including the run-in and intervention periods. Key activities undertaken during each visit are shown in Table 3. Participants will be provided with 24-hour telephone contacts for support if required. Health professionals will log all time taken training and communicating with the study participants.

Table 3: Study visits

Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Weeks from randomisation			-3	-2	-1	0	1	~7	11	12	13	23	24	25	26	26	39
Clinical assessment	X					X					X					X	
Time with health professional		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HbA_{1c}	X					X					X					X	
β-hCG, C-peptide	X																
CHO-counting education		X									X						
Insulin pump training							X										
Insulin dose review		X						X			X					X	
Logbook provision			X														
Logbook data collection				X	X	X	X	X	X	X	X	X	X	X	X	X	
Masked CGM insertion			X	X	X				X	X		X	X	X			
Glucose meter upload				X	X	X	X	X	X	X	X	X	X	X	X	X	
Psychosocial, sleep, cognitive functioning surveys	X										X					X	
Cognitive performance device provision			X						X			X					
Actigraphy & sleep diary provision			X	X	X				X	X		X	X	X			
Semi-structured interviews							X		X							X	X
Driving device and diary provision			X	X	X				X	X		X	X	X			
Holter monitor provision			X						X			X					
Vascular disease risk markers						X										X	

Run-in period

After enrolment, there will be a run-in period lasting at least 5 weeks. Participants will undergo initial medical, psychosocial and cognitive assessments. Their diabetes-related knowledge and carbohydrate-counting proficiency will be assessed and their insulin dosing

will be optimised. Participants will be provided with detailed training and support to use the study glucose meters and masked CGM devices. Education will be provided by diabetes nurse educators and dieticians to optimise participants' diabetes self-management including carbohydrate-counting. The optimisation of carbohydrate-counting is central to baseline optimisation for all participants in the study—this aims to achieve the best possible match of bolus insulin doses to the individuals' requirements for the carbohydrate consumed for both groups, thereby testing the closed-loop aspect of the hybrid closed-loop system's insulin delivery in comparison with standard therapy.

After provision of education, data will be collected for 3 weeks of baseline masked CGM, actigraphy (sleep data) and from the self-reported diabetes logbook. Driving log data (to associate with the CGM data) will also be collected during these 3 weeks for participants at the three clinical sites in Melbourne. At the end of the run-in period, the CGM data will be uploaded and checked to ensure data are available for at least 70% of the time.[41] If the minimum required CGM data are not available, an additional week of CGM will be undertaken to fulfil the protocol requirements. At the end of the run-in, baseline blood and urine samples will be collected for measurement of HbA_{1c} and biochemical markers of vascular disease risk.

Randomisation

Eligible participants will be randomised after completing the run-in. Group allocation will be a 1:1 ratio using minimisation with three variables, all of which are expected to be highly prognostic of the primary outcome. These minimisation variables are: i) the proportion of time-in-target glucose range at baseline (dichotomised to ≤50% and >50%); ii) study centre (seven clinical sites); and iii) insulin delivery modality (MDI or IPT). Randomisation will be performed by an independent group of statisticians using central randomisation software, and will be implemented into an electronic participant record system.

The nature of the study groups does not allow blinding of participants or investigators.

Intervention period

After randomisation, there will be a 26-week intervention period.

Participants randomised to standard therapy will continue using their current insulin delivery modality (MDI or IPT, with bolus calculator in the glucose meter or pump, respectively) and will be instructed to refrain from using RT-CGM during the study.

Participants randomised to hybrid closed-loop therapy will receive general insulin pump and CGM education and training, plus instruction regarding usage of the study hybrid closed-loop system. This education and training period may take up to 4 weeks (likely longer for those using MDI than IPT at baseline). The hybrid closed-loop system will be programmed with participants' usual insulin-to-carbohydrate ratios and insulin sensitivity factors, as well as their usual basal rates (or the basal rates determined by their clinicians for those participants transitioning from MDI). Participants will be provided with a 24-hour technical help telephone contact for the hybrid closed-loop system.

Participants at the three clinical sites in Melbourne who are randomised to hybrid closed-loop therapy will undergo four semi-structured interviews to assess their expectations of, and experiences with, the technology. These interviews will be conducted at randomisation, then at 11 weeks, 26 weeks and 39 weeks post-randomisation.

Participants will have mid-study data collected between 11 weeks to 13 weeks post-randomisation. Two weeks of masked CGM data, cognitive assessments and actigraphy will be collected, plus driving data for participants at the Melbourne sites. Clinical review with assessment of diabetes management and carbohydrate-counting, and adjustment of therapy and further education as required, will be undertaken 13 weeks post-randomisation. At this visit, psychosocial questionnaires will be completed and venous samples for HbA_{1c} will be collected.

Participants will have end-of-study data collected between 23 to 26 weeks post-randomisation. Three weeks of masked CGM data, cognitive assessments and actigraphy will be collected, plus driving data for participants at the Melbourne sites. At the end of the three-week period, the CGM data will be uploaded and checked for available data at least 70% of the time. If 70% of CGM data are not available, an additional week of CGM data will be collected. At the end-of-study visit (26 weeks post-randomisation), psychosocial questionnaires will be completed, and venous and urine samples will be collected for HbA_{1c} and biochemical markers of vascular disease risk. Participants in the hybrid closed-loop group will change back to using their usual insulin delivery modality (MDI or IPT). Doctor visit data from the Medicare Benefits Schedule and insulin prescription data from the Pharmaceutical Benefits Scheme will be accessed for study participants.

Statistical methods

The primary analysis will assess differences in the proportion of time-in-target glucose sensor range (3.9–10.0 mmol/L) with hybrid closed-loop versus standard therapy, measured by masked CGM at 23–26 weeks post-randomisation on an intention-to-treat basis using analysis of covariance (ANCOVA) with adjustment for baseline time-in-target range. A *p*-value threshold of <0.05 will be used to determine statistical significance.

Model fit will be evaluated by exploration of residuals. If the model is of poor fit, the outcome variable will be transformed and the model refitted and evaluated. If unsuccessful, nonparametric analysis will be performed.

Analysis of continuous secondary outcomes will also use ANCOVA with adjustment for baseline time-in-target range, whereas Poisson or negative binomial regression will be used for count outcomes and logistic regression will be used for binary outcomes. Subgroup analysis by baseline insulin delivery modality will be performed by inclusion of an interaction term in the regression modelling or by a stratified analysis when non-parametric methods are used.

No adjustment for multiplicity is planned. All results for primary and secondary outcomes will be reported.[49] No interim analysis is planned.

Health economic evaluation

An economic evaluation will determine the incremental cost of home-based hybrid closed-loop versus standard diabetes therapy in Australia. This analysis will quantify costs directly associated with hybrid closed-loop and standard diabetes therapy plus other impacts on the health system (Table 1). Outcomes will be assessed in quality-adjusted life years for changes in health-related quality of life, and for the likely long-term impact of changes in glucose control on long-term outcomes using a type 1 diabetes simulation model.

Safety assessments

Safety parameters to be assessed include severe hypoglycaemia, ketoacidosis, and unplanned hospitalisations directly related to the study (Table 1).

Efficacy assessments

Efficacy parameters to be assessed include glucose control, clinical measures, psychosocial and cognitive functioning, human-technology interaction, health economic measures and biochemical markers of vascular disease risk (Table 1).

Closed-loop system performance parameters

Closed-loop system performance parameters to be assessed relate to the system overall, to individual system components and to system usability (Table 1).

Trial oversight

The study will be conducted in accordance with the principles of the Declaration of Helsinki and guidelines for Good Clinical Practice (GCP).

The day-to-day study management will be the responsibility of the investigators at each clinical site. The Principal Investigator and study project manager will maintain regular correspondence with all investigators and study coordinators. The Principal Investigator, with the sites' lead investigators, will assume responsibility for the progress of the study in accordance with agreed timelines and milestones with the study funders. A combined data safety and monitoring board (DSMB) will be established for this study and the aligned study, independent from the study investigators, comprising adult and paediatric physicians experienced in statistics and clinical trials. The study project manager will liaise with the study teams in all centres to establish procedures and ensure that the study is carried out according to the protocol and to standards of GCP, with robust systems for reporting adverse events. The study project manager will be responsible for the central preparations of data for presentation to the DSMB.

ETHICS AND DISSEMINATION

The study has received ethics approval from the lead site Human Research Ethics Committee. Other clinical sites provide oversight through local governance committees. Any substantial amendments to the study protocol will be reported to the lead site ethics committee for approval prior to implementation, and updated on the trial registry, with the study investigators being advised in writing.

All potential participants will be provided with written and verbal information regarding the study, the procedures involved and all potential risks related to participating. A study investigator will obtain written informed consent from each participant prior to commencing study procedures. All personal information about potential and enrolled participants will be de-identified to protect confidentiality before, during and after the trial. Standard operating procedures for reporting all adverse events, device-related adverse events and severe adverse events will be in place. The Human Research Ethics Committees and the Therapeutic Goods

Administration of Australia will be informed of any serious adverse events and any unexpected device-related adverse events.

Screening and recruitment commenced in May 2017. It is anticipated that the study visits will be completed by May 2019. The results of the study will be disseminated at national and international conferences and by peer-reviewed publications. Participants will be provided with a summary of the study results by their site's lead investigator.

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Contributors

SAM, MIDB, PGC, AJJ, ACK, JS, GMW, TWJ and DNO designed the study. SAM and DNO drafted the manuscript. SAM, MIDB, VS, MHL, BP, GAR, LAB, MGB, FJC, PMC, NDC, PGC, EAD, JMF, CH, DJH, JCH, AJJ, JK, ACK, BRK, KK, RJM, RWM, JAN, CS, JS, SNS, ST, GMW, SV, TWJ and DNO contributed to the writing and/or critical review of the study protocol and reviewed this manuscript for intellectual content. DNO is the principal investigator and guarantor.

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Competing interests

MIDB and NDC report receiving speaker honoraria from Medtronic. DJH reports receiving speaker and advisory board honoraria from Medtronic. RWM reports receiving conference

travel and accommodation support from Medtronic. JS reports that the ACBRD has received honoraria from Medtronic in relation to her speaking engagements and role in advisory boards. DNO reports receiving speaker honoraria and research grants from Medtronic.

Ethics approval

St Vincent's Hospital Melbourne Human Research Ethics Committee (lead site, approval number HREC-D 088/16).

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FIGURE LEGEND

Figure 1: Study protocol overview

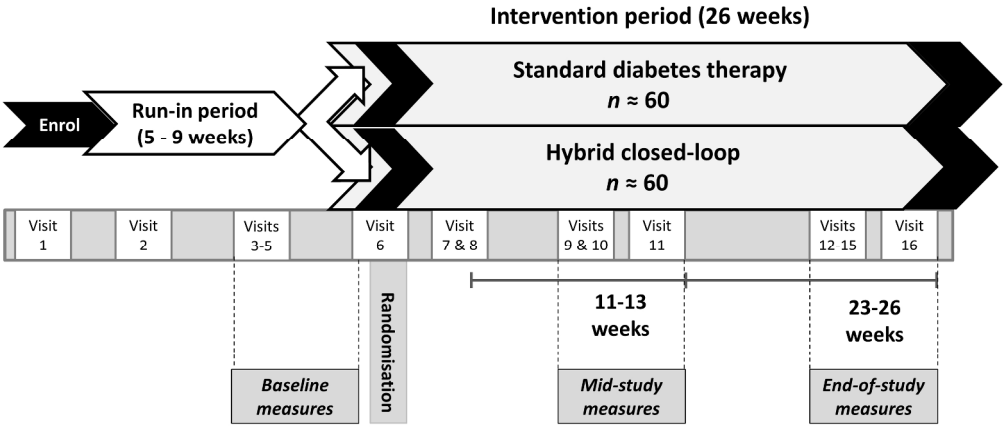

Figure 1: Study protocol overview

254x190mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	1–23
Protocol version	3	Date and version identifier	7
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	2
	5b	Name and contact information for the trial sponsor	2 and 7
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	19

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5–7
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7–8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7 and 11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	15–17
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	19
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7 and 11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8–10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	15

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	13–14
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17–18

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	19
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17–18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	19
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	19

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____19_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____N/A_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	____19_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____20_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____19_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	____N/A_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____20_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____20_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____N/A_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	____Appendix__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____N/A_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

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Secondary Subject Heading:	Medical management, Patient-centred medicine, Pharmacology and therapeutics, Research methods
Keywords:	Type 1 diabetes, Closed loop, Adult

The effect of 6 months hybrid closed-loop insulin delivery in adults with type 1 diabetes: a randomised controlled trial protocol

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ABSTRACT

Introduction

Manual determination of insulin dosing largely fails to optimise glucose control in type 1 diabetes. Automated insulin delivery via closed-loop systems has improved glucose control in short-term studies. The objective of the present study is to determine the effectiveness of 6 months closed-loop compared with manually-determined insulin dosing on time-in-target glucose range in adults with type 1 diabetes.

Methods and analysis

This open-label, seven-centre, randomised controlled parallel group clinical trial will compare home-based hybrid closed-loop versus standard diabetes therapy in Australia. Adults aged ≥25 years with type 1 diabetes using intensive insulin therapy (via multiple daily injections or insulin pump, total enrolment target *n*=120) will undertake a run-in period including diabetes and carbohydrate-counting education, clinical optimisation and baseline data collection. Participants will then be randomised 1:1 either to 26 weeks of MiniMed™ 670G hybrid closed-loop system therapy (Medtronic, Northridge, CA, USA) or continuation of their current diabetes therapy. The hybrid closed-loop system delivers insulin automatically to address basal requirements and correct to target glucose level, while bolus doses for meals require user initiation and carbohydrate estimation. Analysis will be intention-to-treat, with the primary outcome time in continuous glucose monitoring (CGM) target range (3.9–10.0 mmol/L) during the final 3 weeks of intervention. Secondary outcomes include: other CGM parameters, HbA_{1c}, severe hypoglycaemia, psychosocial well-being, sleep, cognition, electrocardiography, costs, quality of life, biomarkers of vascular health and hybrid closed-loop system performance. Semi-structured interviews will assess the expectations and experiences of a sub-group of hybrid closed-loop users.

Ethics and dissemination

The study has Human Research Ethics Committee approval. The study will be conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Results will be disseminated at scientific conferences and via peer-reviewed publications.

Trial registration number

ACTRN12617000520336, pre-results

Strengths and limitations of the study

- Multi-centre, randomised controlled parallel group trial of 26 weeks home-based hybrid closed-loop versus standard therapy
- Broad outcomes will be assessed in addition to glucose control: psychosocial, sleep, cognition, electrocardiography, vascular health biomarkers and health economic measures
- The standard therapy comparator—multiple daily insulin injections or insulin pump therapy, without real-time continuous glucose monitoring—reflects current practice in Australia for most adults with type 1 diabetes, though this may not reflect standard care in other countries
- The study emphasises education and clinical optimisation for all participants pre-randomisation, and the visit schedule is identical for both groups (by design, continuous glucose monitoring information is only available to the closed-loop group)
- This study of adults aged ≥25 years has glucose end-points aligned with a concurrent study examining hybrid closed-loop for young people aged 12 to <25 years, thereby facilitating comparison of metabolic outcomes between the two populations

INTRODUCTION

Advances in type 1 diabetes insulin regimens and glucose monitoring have occurred over recent decades, facilitating improved glucose control and resulting in better health and quality of life.[1-4] The long-term vascular complications of type 1 diabetes are reduced by intensive insulin therapy compared with less intensive therapy.[1 2] Consequently, intensive insulin therapy—with subcutaneous administration via either multiple daily injections (MDI) or insulin pump therapy (IPT)—is a core strategy in current type 1 diabetes management.[5] Nevertheless, even with modern therapies, only 20–30% of adults with type 1 diabetes achieve HbA_{1c} targets[6 7], and long-term vascular complications and reduced life expectancy continue to be a reality for people with type 1 diabetes.[8 9]

Insulin requirements can vary unpredictably. They are impacted by time of day, meals, exercise, illness and antecedent hypoglycaemia. Manual determination of insulin dosing by people with type 1 diabetes requires continuous vigilance to maintain glucose levels within a healthy range. Insulin dosing decisions carry cognitive and emotional burden, and may be inconsistent due to fatigue, distress, fluctuating glucose levels or coexistent fear of hypoglycaemia. Hence, manual determination of insulin dosing represents an imperfect strategy to optimise glucose control. Further advances in technology are required to improve the match of insulin delivered to individuals' varying insulin requirements, and to minimise the burden of type 1 diabetes.

Closed-loop systems are designed to maintain glucose levels at a predetermined target by linking continuous glucose monitoring (CGM) information with an insulin dosing algorithm for automated subcutaneous insulin delivery by a pump.[10] These systems are being developed to address the need for improving glucose control while reducing the burden associated with treatment regimens. There is increasing scientific literature of randomised controlled studies reporting improved glucose control with short-term use of closed-loop systems (up to 3 months) compared with conventional insulin pumps.[11-15] A recent meta-analysis of outpatient randomised controlled trials with intervention periods ranging from 4 days to 12 weeks reported that single-hormone (insulin alone) closed-loop systems improve time-in-target glucose range and reduce time spent in hypoglycaemia compared with conventional IPT (with/without CGM).[16] Overall, time-in-target glucose range had a mean (95% confidence interval) absolute increase of 11.1% (6.9, 15.2), and the time spent in hypoglycaemia had an absolute reduction of 1.9% (0.4, 3.4). Studies in this meta-analysis used 'hybrid closed-loop' systems with automated insulin delivery to address basal requirements and correct to target

glucose, and user-initiated bolus insulin to address carbohydrate consumption. Results from a short-term randomised crossover study challenging a closed-loop system with both moderate- and high-intensity exercise indicated that closed-loop glucose control was safe; only a single episode of mild hypoglycaemia occurred and marked hyperglycaemic excursions were limited.[17] In an uncontrolled study, there were no safety concerns when 14 participants used free-living closed-loop 24/7 for 6 months.[18]

For individuals with type 1 diabetes, both hypoglycaemia and hyperglycaemia can affect physical and emotional well-being, quality of life, and activities of daily living such as driving.[4 19-21] Moreover, type 1 diabetes places significant burden on caregivers, families, workplaces and health services.[22-24] Closed-loop technology has shown promise to address the limitations of current therapy in relation to these burdens.[25] Qualitative and small-scale quantitative sub-studies in closed-loop trials have shown user acceptability and treatment satisfaction are high with closed-loop systems in home settings, particularly for overnight use when there is minimal manual interaction for meals and activity.[26-28] Although intrusive device alerts, device size and technical difficulties can negatively affect the overall experience, users typically report benefits outweighing annoyances, which they anticipate will be overcome with future iterations of the technology.[27-29] However, the only published randomised closed-loop trial involving adults to have included established, validated psychological measures, reported no between-group differences in treatment satisfaction or fear of hypoglycaemia.[30]

HbA_{1c}, a measurement of average glycaemia during the preceding 10–12 weeks, predicts the risk of developing long-term complications and is valuable for assessing glycaemic trends in populations over time.[1 2 31] However, HbA_{1c} cannot provide information about glucose variability or time-in-target glucose range, and is even considered an unreliable indicator of an individual's mean glucose.[32] A recent large longitudinal registry study reported lower cardiovascular and all-cause mortality in individuals using IPT compared with MDI, even without between-group differences in HbA_{1c}.[33] The mortality difference observed may have been attributable to factors such as time-in-target glucose range or glucose variability (not reflected in HbA_{1c}). Consequently, HbA_{1c} may be of limited value in comparison with CGM when assessing an individual's glucose levels in response to automated closed-loop insulin delivery.

With short-term randomised controlled studies of closed-loop systems (conducted in camp/hotel and home settings) demonstrating improvements in glucose control,[16] it remains

to be determined whether these findings are sustained in the longer term in the home setting and whether diabetes-related vascular complications may be influenced. Longer-term randomised controlled home-based studies—with closed-loop implemented day and night—are required. In addition, the impact of closed-loop insulin delivery on patient-reported outcomes such as fear of hypoglycaemia, treatment satisfaction, sleep quality and cognition remains a significant gap in the evidence base.[34] Finally, the benefits associated with this new technology need to be balanced against its cost.

In Australia, the government presently subsidises the purchase of insulin, injection needles, blood glucose monitoring strips and insulin pump delivery consumables for people with type 1 diabetes.[35] Insulin pumps are not government-subsidised, but are available via either direct purchase or in conjunction with a private health insurance fund. CGM is government-subsidised only for eligible individuals under 21 years of age.[36] As a result, only a small fraction of adults with type 1 diabetes use CGM on a regular basis. Hence, standard diabetes therapy for adults in Australia currently involves subcutaneous intensive insulin therapy delivered via either MDI or pump, together with finger-prick blood glucose monitoring.

We hypothesise that hybrid closed-loop insulin delivery compared with manually-determined insulin dosing (without CGM) will improve time-in-target glucose range for adults with type 1 diabetes. The overall aim of the study is to evaluate the effect of 6 months of hybrid closed-loop insulin delivery on glucose control, psychosocial well-being, sleep quality, cognition and markers of vascular disease risk compared with standard diabetes therapy for adults with type 1 diabetes.

METHODS AND ANALYSIS

Overview

This open-label, randomised controlled parallel group clinical trial will compare 26 weeks of hybrid closed-loop therapy versus 'standard therapy' for 120 adults (aged ≥25 years) with type 1 diabetes (protocol version 2.0, dated 29 March 2017). The standard therapy comparator consists of insulin delivered via either MDI or IPT, without real-time continuous glucose monitoring (RT-CGM), and was chosen to reflect current self-management of type 1 diabetes among adults in Australia.

The study is being conducted at seven university hospitals across Australia. The University of Melbourne is the coordinating academic institution, with St Vincent's Hospital Melbourne (Melbourne) the study sponsor and lead clinical site. Other clinical sites are: Flinders Medical

Centre (Adelaide), Royal Hobart Hospital (Hobart), Royal Melbourne Hospital (Melbourne), Sir Charles Gairdner Hospital (Perth), The Alfred and Baker Heart and Diabetes Institute (Melbourne) and Westmead Hospital (Sydney). Other academic institutions involved are Sydney University and Deakin University. In parallel, a similar study of younger people (aged 12 to <25 years) with type 1 diabetes is being undertaken in Australia; the hybrid closed-loop system and primary outcome are aligned for the two studies.

Study outcomes

The study outcomes are listed in Table 1.

Table 1: Study outcomes

Primary outcome

The proportion of time sensor glucose is in target range (3.9–10.0 mmol/L) with hybrid closed-loop versus standard therapy (MDI or IPT without RT-CGM), measured by masked CGM at 23–26 weeks post-randomisation.

Secondary outcomes

Hybrid closed-loop therapy versus standard therapy (overall and for each of baseline MDI and IPT separately) for the measures listed below.

1. Glucose control:
   a. Masked CGM metrics for 24 h/day, day [06:00–00:00] and night [00:00–06:00] (measured at mid-study, end-of-study, and mid-study plus end-of-study combined):
      i. Proportion of time spent 3.9–10.0 mmol/L (excluding the primary outcome)
      ii. Proportion of time spent <2.8 mmol/L
      iii. Proportion of time spent <3.3 mmol/L
      iv. Proportion of time spent <3.9 mmol/L
      v. Proportion of time spent 3.9–7.8 mmol/L
      vi. Proportion of time spent >10.0 mmol/L
      vii. Proportion of time spent >13.9 mmol/L
      viii. Proportion of time spent >16.7 mmol/L
      ix. SD and coefficient of variation
      x. Mean glucose
   b. Fasting capillary blood glucose
   c. HbA_{1c}
   d. 1,5-anhydroglucitol
   e. Symptomatic hypoglycaemia (with blood glucose <3.5 mmol/L) requiring carbohydrate rescue (*n*)
2. Clinical:
   a. Change in total daily dose of insulin, and basal/bolus proportions
   b. Change in insulin-to-carbohydrate ratio
   c. Change in body weight
3. Psychosocial, sleep and cognitive functioning:
   a. Treatment satisfaction: The Diabetes Treatment Satisfaction Questionnaire (DTSQ) status

and change versions
   b. Satisfaction with technology: Diabetes Management Experiences Questionnaire (DME-Q)
   c. Fear of hypoglycaemia: Hypoglycaemia Fear Survey short form (HFS-SF)
   d. Fear of hyperglycaemia: Hyperglycaemia Avoidance Scale (HAS)
   e. Hypoglycaemia Awareness: Gold Score
   f. Diabetes distress: Problem Areas in Diabetes (PAID)
   g. Diabetes-specific quality of life: DAWN Impact of Diabetes profile (DIDP)
   h. Diabetes-specific positive well-being: Well-being Questionnaire (W-BQ28) Positive Diabetes Well-being Subscale
   i. Cognitive function: Prospective and Retrospective Memory Questionnaire (PRMQ) and Psychomotor Vigilance Task (PVT-192)
   j. Driving: proportion of time-in-target glucose range while driving (Melbourne sites only)
   k. Sleep quality: Actigraph data, Pittsburgh Sleep Quality Index, Karolinska Sleepiness Scale
4. Electrocardiograph profile (via Holter monitor)
   a. Corrected QT interval (QT_c)
   b. Heart rate
   c. Cardiac arrhythmias
5. Human-technology interaction (participants using hybrid closed-loop system):
   a. Participant perceptions of the hybrid closed-loop system assessed via SMS data collection
   b. Participant expectations and experiences with the hybrid closed-loop system assessed via longitudinal semi-structured interviews (Melbourne sites only)
6. Health economic:
   a. Quality-adjusted life years calculated from the EQ-5D-5L
   b. Hypoglycaemic events and HbA_{1c}
   c. Participant and family reporting on work interruption
   d. Reported time spent on training, education and support, by the type of health professional resource used
   e. Diabetes management consumables (glucose strips, ketone strips, batteries, sensors, site dressings, lancets, needles, insulin)
   f. Resource utilisation tracked via linked administrative data from the Australian Medicare Benefits Schedule and Pharmaceutical Benefits Scheme
7. Biochemical markers of vascular disease risk:
   a. Cell adhesion molecules
   b. Oxidised low-density lipoprotein
   c. Myeloperoxidase
   d. MicroRNA signatures for arterial, renal and retinal complications
   e. Telomerase
   f. DNA methylation/acetylation
   g. Isoprostanes (blood and urine) and proteomics
   h. Clotting profile
8. Hybrid closed-loop system performance parameters:
   a. Proportion of time closed-loop active
   b. Unplanned exits from closed-loop (*n*)
   c. Sensor performance versus blood glucose meter as measured by MARD and sensor failures (*n*)
   d. Reported insulin delivery line failures (*n*)
   e. Participant calls to the technical help line (*n*)

9. Safety:
   a. Hospitalisations for diabetic ketoacidosis (*n*)
   b. Severe hypoglycaemia, defined as hypoglycaemia requiring the assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions (*n*)

The primary study outcome is the proportion of sensor glucose time-in-target range (3.9–10.0 mmol/L) with hybrid closed-loop versus standard therapy, measured by masked CGM 23–26 weeks post-randomisation. This primary end-point was selected to provide the best indication of individual participants' glucose control. The 3.9–10.0 mmol/L glucose range is aligned with outcome metrics proposed by the JDRF Artificial Pancreas Project Consortium, is consistent with available data relating glucose control and complication prevention, and represents a realistic glucose target.[32 37] The secondary outcomes are listed in Table 1 (row 2), sections 1 to 9.

CGM study outcome data will be collected by identical methods for participants in both groups. Hence, participants assigned hybrid closed-loop therapy will wear two identical glucose sensors for 2 weeks mid-study and 3 weeks at end-of-study—one sensor providing RT-CGM information to the user and directly linking to the hybrid closed-loop system, and a second sensor collecting masked CGM study outcome data. The closed-loop system performance parameters chosen as study outcome measures are based upon an international consensus report for outcomes measures in closed-loop trials.[37]

For closed-loop technology to achieve long-term clinical benefits, then in addition to positively impacting biomedical outcomes, user acceptance, uptake and adaptations are required.[28 38] Therefore, this study will assess aspects of psychosocial well-being via both subjective (questionnaires, interviews) and objective (actigraph, psychomotor task) methods. This holistic approach will progress understanding of the human factors involved, thereby enabling adaption of the technology in line with the person's expectations and experiences.[39] The study will also assess whether CGM has an impact on utilisation of health services and medications.

Eligibility

Inclusion and exclusion criteria for participation are listed in Table 2.

Table 2: Eligibility

Inclusion criteria
• Type 1 diabetes (as defined by the American Diabetes Association)[40] for at least 1 year
• Insulin regimen consisting of either:
o MDI with ≥4 injections per day (including ≥3 rapid-acting insulin injections and ≥1 long-acting insulin injection); or
o IPT established for ≥3 months
• Age 25–70 years inclusive
• HbA1c ≤10.5% (≤91 mmol/mol)
• Living in an area with internet and cellular phone coverage
• English speaking proficiency
Exclusion criteria
• Chronic kidney disease (eGFR <45 mL/min/1.73m^2)
• Current use of RT-CGM (defined as use >25% of the time during the past 3 months)
• Use of any non-insulin glucose-lowering agent within the past 3 months
• Oral or injected steroid use within the past 3 months
• Pregnancy, or pregnancy planned within study period
• Untreated coeliac disease or other malabsorption
• Uncontrolled thyroid disease
• Clinically-significant gastroparesis
• Uncontrolled hypertension (blood pressure: diastolic >100 or systolic >160 mmHg)
• History of myocardial infarction, severe uncontrolled heart failure, unstable angina, transient ischaemic attack, stroke, or thromboembolic disease in the past 3 months
• Poor visual acuity precluding use of the study technology
• Inability or unwillingness to meet protocol requirements
• Any severe or unstable medical or psychological condition which, in the opinion of the investigator, would compromise the ability to meet protocol requirements

The minimum inclusion age of 25 years was chosen to reflect a general adult population with type 1 diabetes while avoiding potential confounders associated with adolescence and emerging adulthood. This decision was informed by results of previous type 1 diabetes CGM and closed-loop studies, where individuals aged <25 years differed from those aged ≥25 years.[14 41]

Use of RT-CGM >25% of the time precludes inclusion. This decision was informed by study findings that adults aged ≥25 years with type 1 diabetes using RT-CGM with warning alarms had improved glucose control without increase in biochemical hypoglycaemia only when RT-CGM was worn ≥5–6 days/week.[41-43] When CGM is used less often or without warning alarms, evidence suggests no glucose control benefit.

Study diabetes management devices

Hybrid closed-loop system

The study hybrid closed-loop is the MiniMed™ 670G system, comprising a glucose sensor and transmitter coupled with an insulin pump containing a closed-loop algorithm (Medtronic, Northridge, CA, USA), and rapid-acting analogue insulin (either insulin aspart or insulin lispro) delivered subcutaneously. CGM data are transmitted to the pump every 5 minutes and the algorithm calculates the basal insulin dose (delivered at 5 min intervals) required to maintain the target glucose level. The algorithm uses a modified proportional integrative derivative model with insulin feedback based on an insulin delivery algorithm originally developed by Steil et al.[44] The algorithm also incorporates a supervisory model predictive component aiming to avoid insulin over-delivery.[45] For meals, the user estimates the amount of carbohydrate to be consumed (entering this into the pump) and checks their capillary blood glucose level. Using this information, an insulin bolus is calculated and delivered according to the individualised insulin-to-carbohydrate ratio and an insulin sensitivity factor determined by the algorithm (should a correction bolus be required).

The MiniMed™ 670G system has been deemed safe and effective for glucose control in a 3-month uncontrolled study [46 47] and an exercise study.[17] The system was approved for use by the US Food and Drug Administration in 2016.

Masked CGM

CGM data masked to both the participants and research team will be collected for study outcome measurements at three time-points: baseline pre-randomisation (3 weeks), mid-study (2 weeks) and end-of-study (3 weeks). For participants randomised to hybrid closed-loop, this masked CGM data collection will be in addition to the system's RT-CGM. The study uses Guardian™ Sensor 3 glucose sensors (Medtronic, Northridge, CA, USA). This sensor configuration has reported performance parameters of mean absolute relative difference (MARD) ± standard deviation (SD) of 9.6% ± 9.0% and mean functional sensor life of 146 ± 39 h when used with a Medtronic MiniMed™ 640G insulin pump.[48] By using a separate

device to collect CGM study outcome data, the device under investigation is not also being used to evaluate its own performance.

For masked CGM data collection, the glucose sensor will be inserted and the sensor recorder will be connected by the study team. During masked CGM, participants will be required to test capillary blood glucose levels at least 4 times per day with a CONTOUR® NEXT LINK meter (details below). Masked CGM data are collected retrospectively by uploading the recorder and the meter.

Blood glucose monitoring

All participants will be provided with a CONTOUR® NEXT LINK 2.4 blood glucose meter (Ascensia, Parsippany, NJ, USA) which is able to transmit data directly to the MiniMed™ 670G insulin pump. Pre-randomisation and for participants randomised to standard therapy, the CONTOUR® NEXT LINK 2.4 will be used in addition to their regular glucose meter during masked CGM. Use of the same glucose meter within the hybrid closed-loop system and for masked CGM calibration will standardise data collection.

Participants using MDI at enrolment will also be provided with an ACCU-CHEK® Aviva Expert blood glucose meter (Roche Diagnostics, Mannheim, Germany), selected for its in-built 'bolus calculator'. The bolus calculator uses the measured blood glucose level, calculated rapid-acting 'insulin on board', and the programmed insulin sensitivity factor and insulin-to-carbohydrate ratio to determine the recommended insulin bolus doses. The use of a meter with bolus calculator by those in the control group who continue with MDI will reflect the bolus calculators used by participants randomised to hybrid closed-loop therapy and by those using IPT randomised to standard diabetes therapy.

Diabetes management software

CareLink™, an internet-based platform from Medtronic, will be used for uploading insulin pump, glucose sensor and glucose meter data. The hybrid closed-loop system data are uploaded to a computer via the system's glucose meter USB connection; insulin pump, sensor and meter data are then accessible to study investigators.

Study design

This is a prospective, open-label, parallel design randomised controlled study involving adults with type 1 diabetes (overall target n=120, with ≥40% using MDI and ≥40% using IPT). Study procedures will be undertaken by medical doctors with sub-speciality training in endocrinology, diabetes nurse educators, dieticians and research nurses. Throughout the

study, the time taken for participant education, training, clinical care and technical support will be recorded; the health professional time will be used in health economic analyses to determine implications for closed-loop becoming a mainstream therapy. Adherence to study protocols will be assessed at each study visit; verbal and written reminders of study instructions will be provided to improve protocol adherence. Participants will continue their usual diabetes clinical care with their treating clinicians during study participation. Participants will be randomised 1:1 either to hybrid closed-loop therapy or to continue using their current standard diabetes therapy (either MDI or IPT) for 26 weeks (Fig. 1). Use of RT-CGM will not be permitted during run-in or by participants randomised to standard diabetes therapy (though CGM without live alerts, e.g. Abbott FreeStyle® Libre, is permissible).

Patient involvement

Investigator discussions with patients throughout provision of clinical care and during previous research studies were taken into consideration when designing this study protocol. The burden of the study intervention will be assessed via SMS data collection and during semi-structured interviews (see Table 1, sections 5a and 5b).

Sample size

The power calculation is for a parallel study design with two groups of equal size. It is based on SDs of the percentage time-in-target glucose range at 6 months (adjusted for baseline) observed for the subset of participants in two randomised clinical trials from the JDRF Study Group who had similar characteristics to participants being recruited here (Professor Roy Beck, personal communication). The SD (95% confidence interval) for pump users was 9% (8%, 12%) and for MDI users was 10% (7%, 19%).

From an initial overall sample size of n=120, with a dropout rate of 10%, a common SD of 9% and a type I error rate of 5%, the power to detect a minimum absolute difference of 5% time-in-target glucose range would be 80%. A more conservative scenario with a dropout rate of 20%, and unequal SDs of 12% and 19% for pump and MDI users, respectively, increases the minimum detectable absolute difference to 9% with power of 80%.

Study schedule

The study will consist of 16 visits including the run-in and intervention periods. Key activities undertaken during each visit are shown in Table 3. Participants will be provided with 24-hour telephone contacts for support if required. Health professionals will log all time taken training and communicating with the study participants.

Table 3: Study visits

Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Weeks from randomisation			-3	-2	-1	0	1	~7	11	12	13	23	24	25	26	26	39
Clinical assessment	X					X					X					X	
Time with health professional		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HbA_{1c}	X					X					X					X	
β-hCG, C-peptide	X																
CHO-counting education		X									X						
Insulin pump training							X										
Insulin dose review		X						X			X					X	
Logbook provision			X														
Logbook data collection				X	X	X	X	X	X	X	X	X	X	X	X	X	
Masked CGM insertion			X	X	X				X	X		X	X	X			
Glucose meter upload				X	X	X	X	X	X	X	X	X	X	X	X	X	
Psychosocial, sleep, cognitive functioning surveys	X										X					X	
Cognitive performance device provision			X						X			X					
Actigraphy & sleep diary provision			X	X	X				X	X		X	X	X			
Semi-structured interviews							X		X							X	X
Driving device and diary provision			X	X	X				X	X		X	X	X			
Holter monitor provision			X						X			X					
Vascular disease risk markers						X										X	

Run-in period

After enrolment, there will be a run-in period lasting at least 5 weeks. Participants will undergo initial medical, psychosocial and cognitive assessments. Their diabetes-related knowledge and carbohydrate-counting proficiency will be assessed and their insulin dosing

will be optimised. Participants will be provided with detailed training and support to use the study glucose meters and masked CGM devices. Education will be provided by diabetes nurse educators and dieticians to optimise participants' diabetes self-management including carbohydrate-counting. The optimisation of carbohydrate-counting is central to baseline optimisation for all participants in the study—this aims to achieve the best possible match of bolus insulin doses to the individuals' requirements for the carbohydrate consumed for both groups, thereby testing the closed-loop aspect of the hybrid closed-loop system's insulin delivery in comparison with standard therapy.

After provision of education, data will be collected for 3 weeks of baseline masked CGM, actigraphy (sleep data) and from the self-reported diabetes logbook. Driving log data (to associate with the CGM data) will also be collected during these 3 weeks for participants at the three clinical sites in Melbourne. At the end of the run-in period, the CGM data will be uploaded and checked to ensure data are available for at least 70% of the time.[41] If the minimum required CGM data are not available, an additional week of CGM will be undertaken to fulfil the protocol requirements. At the end of the run-in, baseline blood and urine samples will be collected for measurement of HbA_{1c} and biochemical markers of vascular disease risk.

Randomisation

Eligible participants will be randomised after completing the run-in. Group allocation will be a 1:1 ratio using minimisation with three variables, all of which are expected to be highly prognostic of the primary outcome. These minimisation variables are: i) the proportion of time-in-target glucose range at baseline (dichotomised to ≤50% and >50%); ii) study centre (seven clinical sites); and iii) insulin delivery modality (MDI or IPT). Randomisation will be performed by an independent group of statisticians using central randomisation software, and will be implemented into an electronic participant record system.

The nature of the study groups does not allow blinding of participants or investigators.

Intervention period

After randomisation, there will be a 26-week intervention period.

Participants randomised to standard therapy will continue using their current insulin delivery modality (MDI or IPT, with bolus calculator in the glucose meter or pump, respectively) and will be instructed to refrain from using RT-CGM during the study.

Participants randomised to hybrid closed-loop therapy will receive general insulin pump and CGM education and training, plus instruction regarding usage of the study hybrid closed-loop system. This education and training period may take up to 4 weeks (likely longer for those using MDI than IPT at baseline). The hybrid closed-loop system will be programmed with participants' usual insulin-to-carbohydrate ratios and insulin sensitivity factors, as well as their usual basal rates (or the basal rates determined by their clinicians for those participants transitioning from MDI). Participants will be provided with a 24-hour technical help telephone contact for the hybrid closed-loop system.

Participants at the three clinical sites in Melbourne who are randomised to hybrid closed-loop therapy will undergo four semi-structured interviews to assess their expectations of, and experiences with, the technology. These interviews will be conducted at randomisation, then at 11 weeks, 26 weeks and 39 weeks post-randomisation.

Participants will have mid-study data collected between 11 weeks to 13 weeks post-randomisation. Two weeks of masked CGM data, cognitive assessments and actigraphy will be collected, plus driving data for participants at the Melbourne sites. Clinical review with assessment of diabetes management and carbohydrate-counting, and adjustment of therapy and further education as required, will be undertaken 13 weeks post-randomisation. At this visit, psychosocial questionnaires will be completed and venous samples for HbA_{1c} will be collected.

Participants will have end-of-study data collected between 23 to 26 weeks post-randomisation. Three weeks of masked CGM data, cognitive assessments and actigraphy will be collected, plus driving data for participants at the Melbourne sites. At the end of the three-week period, the CGM data will be uploaded and checked for available data at least 70% of the time. If 70% of CGM data are not available, an additional week of CGM data will be collected. At the end-of-study visit (26 weeks post-randomisation), psychosocial questionnaires will be completed, and venous and urine samples will be collected for HbA_{1c} and biochemical markers of vascular disease risk. Participants in the hybrid closed-loop group will change back to using their usual insulin delivery modality (MDI or IPT). Doctor visit data from the Medicare Benefits Schedule and insulin prescription data from the Pharmaceutical Benefits Scheme will be accessed for study participants.

Statistical methods

The primary analysis will assess differences in the proportion of time-in-target glucose sensor range (3.9–10.0 mmol/L) with hybrid closed-loop versus standard therapy, measured by masked CGM at 23–26 weeks post-randomisation on an intention-to-treat basis using analysis of covariance (ANCOVA) with adjustment for baseline time-in-target range. A *p*-value threshold of <0.05 will be used to determine statistical significance.

Model fit will be evaluated by exploration of residuals. If the model is of poor fit, the outcome variable will be transformed and the model refitted and evaluated. If unsuccessful, nonparametric analysis will be performed.

Analysis of continuous secondary outcomes will also use ANCOVA with adjustment for baseline time-in-target range, whereas Poisson or negative binomial regression will be used for count outcomes and logistic regression will be used for binary outcomes. Subgroup analysis by baseline insulin delivery modality will be performed by inclusion of an interaction term in the regression modelling or by a stratified analysis when non-parametric methods are used.

No adjustment for multiplicity is planned. All results for primary and secondary outcomes will be reported.[49] No interim analysis is planned.

Health economic evaluation

An economic evaluation will determine the incremental cost of home-based hybrid closed-loop versus standard diabetes therapy in Australia. This analysis will quantify costs directly associated with hybrid closed-loop and standard diabetes therapy plus other impacts on the health system (Table 1). Outcomes will be assessed in quality-adjusted life years for changes in health-related quality of life, and for the likely long-term impact of changes in glucose control on long-term outcomes using a type 1 diabetes simulation model.

Safety assessments

Safety parameters to be assessed include severe hypoglycaemia, ketoacidosis, and unplanned hospitalisations directly related to the study (Table 1).

Effectiveness assessments

Effectiveness parameters to be assessed include glucose control, clinical measures, psychosocial and cognitive functioning, human-technology interaction, health economic measures and biochemical markers of vascular disease risk (Table 1).

Closed-loop system performance parameters

Closed-loop system performance parameters to be assessed relate to the system overall, to individual system components and to system usability (Table 1).

Trial oversight

The study will be conducted in accordance with the principles of the Declaration of Helsinki and guidelines for Good Clinical Practice (GCP).

The day-to-day study management will be the responsibility of the investigators at each clinical site. The Principal Investigator and study project manager will maintain regular correspondence with all investigators and study coordinators. The Principal Investigator, with the sites' lead investigators, will assume responsibility for the progress of the study in accordance with agreed timelines and milestones with the study funders. A combined data safety and monitoring board (DSMB) will be established for this study and the aligned study, independent from the study investigators, comprising adult and paediatric physicians experienced in statistics and clinical trials. The study project manager will liaise with the study teams in all centres to establish procedures and ensure that the study is carried out according to the protocol and to standards of GCP, with robust systems for reporting adverse events. The study project manager will be responsible for the central preparations of data for presentation to the DSMB.

ETHICS AND DISSEMINATION

The study has received ethics approval from the lead site Human Research Ethics Committee. Other clinical sites provide oversight through local governance committees. Any substantial amendments to the study protocol will be reported to the lead site ethics committee for approval prior to implementation, and updated on the trial registry, with the study investigators being advised in writing.

All potential participants will be provided with written and verbal information regarding the study, the procedures involved and all potential risks related to participating. A study investigator will obtain written informed consent from each participant prior to commencing study procedures. All personal information about potential and enrolled participants will be de-identified to protect confidentiality before, during and after the trial. Standard operating procedures for reporting all adverse events, device-related adverse events and severe adverse events will be in place. The Human Research Ethics Committees and the Therapeutic Goods

Administration of Australia will be informed of any serious adverse events and any unexpected device-related adverse events.

Screening and recruitment commenced in May 2017. It is anticipated that the study visits will be completed by May 2019. The results of the study will be disseminated at national and international conferences and by peer-reviewed publications. Participants will be provided with a summary of the study results by their site's lead investigator.

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Contributors

SAM, MIDB, PGC, AJJ, ACK, JS, GMW, TWJ and DNO designed the study. SAM and DNO drafted the manuscript. SAM, MIDB, VS, MHL, BP, GAR, LAB, MGB, FJC, PMC, NDC, PGC, EAD, JMF, CH, DJH, JCH, AJJ, JK, ACK, BRK, KK, RJM, RWM, JAN, CS, JS, SNS, ST, GMW, SV, TWJ and DNO contributed to the writing and/or critical review of the study protocol and reviewed this manuscript for intellectual content. DNO is the principal investigator and guarantor.

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Competing interests

MIDB and NDC report receiving speaker honoraria from Medtronic. DJH reports receiving speaker and advisory board honoraria from Medtronic. RWM reports receiving conference

travel and accommodation support from Medtronic. JS reports that the ACBRD has received honoraria from Medtronic in relation to her speaking engagements and role in advisory boards. DNO reports receiving speaker honoraria and research grants from Medtronic.

Ethics approval

St Vincent's Hospital Melbourne Human Research Ethics Committee (lead site, approval number HREC-D 088/16).

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FIGURE LEGEND

Figure 1: Study protocol overview

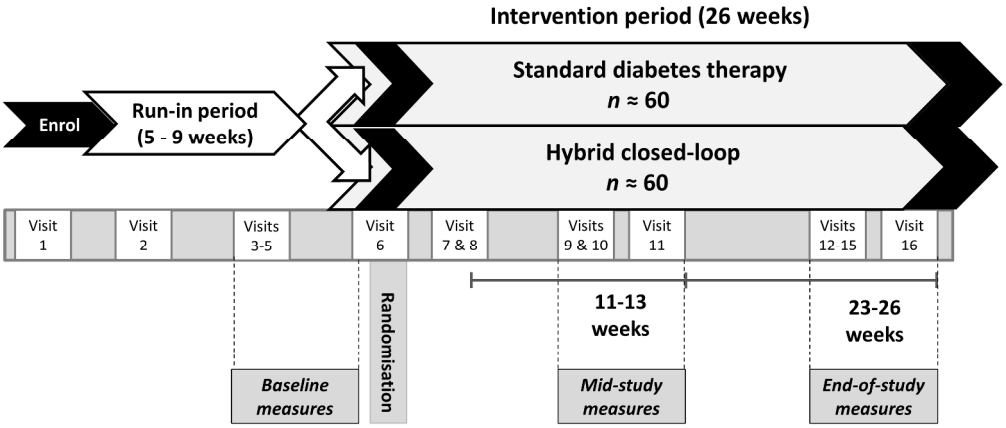

Figure 1: Study protocol overview

254x190mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	1–23
Protocol version	3	Date and version identifier	7
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	2
	5b	Name and contact information for the trial sponsor	2 and 7
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	19

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5–7
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7–8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7 and 11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	15–17
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	19
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7 and 11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8–10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	15

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	13–14
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17–18

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	19
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17–18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	19
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	19

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____19_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____N/A_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	____19_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____20_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____19_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	____N/A_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____20_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____20_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____N/A_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	____Appendix__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____N/A_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.