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Study protocol for a randomised open label clinical trial examining the safety and efficacy of the Android Artificial Pancreas System (AAPS) with advanced bolus-free features in adults with type 1 diabetes: the 'CLOSE IT' (Closed Loop Open SourcE In Type 1 diabetes) trial

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ABSTRACT

Introduction: Multiple automated insulin delivery (AID) systems have become commercially available following randomised controlled trials demonstrating benefit in people with type 1 diabetes (T1D). However, their real-world utility may be undermined by user-associated burdens, including the need to carbohydrate count and deliver manual insulin boluses. There is an important need for a "fully-automated closed loop" (FCL) AID system, without manual mealtime boluses. The (Closed Loop Open SourcE In Type 1 diabetes) CLOSE IT trial is a randomised trial comparing a FCL AID system to the same system used as hybrid closed loop (HCL) in people with T1D, in an outpatient setting over an extended timeframe.

Methods and analysis: Randomised, open-label, parallel, non-inferiority trial comparing the Android Artificial Pancreas System (AAPS) AID algorithm used as FCL to the same algorithm used as HCL. Seventy-five participants aged 18-70 will be randomised (1:1) to one of two treatment arms for 12 weeks: (a) FCL – participants will be advised not to bolus for meals; (b) HCL – participants will use the AAPS AID algorithm as HCL with announced meals. The primary outcome is the percentage of time in target sensor glucose range (3.9-10.0mmol/L) (TIR). Secondary outcomes include other glycaemic metrics, safety, psychosocial factors, platform performance, and user dietary factors. Twenty FCL arm participants will participate in a 4-week extension phase comparing glycaemic and dietary outcomes using NovoRapid® (insulin aspart) to Fiasp® (insulin aspart and niacinamide).

Ethics and dissemination: Approvals are by the Alfred Health Ethics Committee (615/22) (Australia) and Health and Disability Ethics Committees (2022 FULL 13832) (New Zealand). Each participant will provide written informed consent. Data protection and confidentiality will be ensured. Study results will be disseminated by publications, conferences and patient advocacy groups.

Trial registration number: ACTRN12622001400752p.

ARTICLE SUMMARY

Strengths and limitations of this study

- CLOSE IT is a direct comparison of an automated insulin delivery (AID) system used as full closed loop (FCL) to that same system used as hybrid closed loop (HCL), in people with T1D during prolonged (12 weeks) outpatient follow-up.
- A 12-week run-in phase aims to ensure all participants are established on AID with optimised skills and pump parameters pre-randomisation.
- Dietary records and qualitative interviews will explore changes in dietary intake and attitudes in FCL system users.
- This trial is unmasked, with participants in both arms having access to the same devices, therefore there is a risk of spuriously concluding non-inferiority due to participant non-adherence.
- The investigational AID system is open-source, therefore trial findings may not apply to people with T1D and diabetes healthcare providers who prefer a commercially available AID system.

INTRODUCTION

Type 1 diabetes (T1D) is a chronic health condition with substantial self-management demands regarding lifestyle, diet, and insulin dosing. Despite technological advances including continuous glucose monitoring (CGM) and insulin pump therapy, most people with T1D do not attain glycaemic targets (1), exposing them to risk of acute and chronic complications. Automated insulin delivery (AID) systems, also termed closed loop or artificial pancreas systems combine insulin pump technology, CGM, and control algorithms, to automatically adjust insulin delivery based on interstitial fluid glucose sensor readings (2). Multiple AID systems have become commercially available following large randomised controlled trials demonstrating improved glycaemia in people with T1D when compared to sensor-augmented pump therapy (SAPT) (3-7). Participants in these trials delivered manual insulin boluses pre-meals and real-world users are advised to do the same, hence these systems are termed “hybrid closed loop” (HCL).

Despite clear glycaemic benefits, real-world utility of AID systems may be undermined by the burden associated with their use. Notably, reluctance to start AID, and AID discontinuation once started, have been reported as more prevalent in users with suboptimal baseline glycaemia (8, 9). Reducing inequity in diabetes outcomes therefore requires minimisation of perceived and actual burdens of AID use. The burden is multifactorial, including device-related factors (10) and difficulty trusting automated insulin dosing decisions (10-14). However, the need to deliver manual insulin boluses with carbohydrate counting is likely to be contributory in many users. Observational T1D studies have described frequent missed mealtime boluses in pump-users (15, 16), and inaccuracies in carbohydrate counting (17, 18). There is therefore an important need for an AID system which can be used as “fully-automated closed loop” (FCL), without manual mealtime boluses.

The oref1 “reference design” algorithm introduced in OpenAPS (open-source artificial pancreas system) is also used in Android Artificial Pancreas System (AAPS) installed as an application on an Android phone. These “do-it-yourself” AID systems were first shared as open-source software in 2015 (19). The CREATE trial (n=97) found that those with T1D using oref1 for 24 weeks in an outpatient setting had higher mean time in range (TIR; percentage of CGM recordings between 3.9-10.0 mmol/L) compared to those using SAPT (71.2 vs. 54.5%, p<0.001) (20). Results broadly aligned with comparable trials of commercial AID systems (3-7). Furthermore, a pilot crossover trial comparing oref1 used as FCL to the same system used as HCL in adolescents with T1D during supervised 3-day periods found no significant difference in mean TIR (81 vs. 83%) (21). Further investigation is required to assess if these findings extrapolate to unselected patients in an unsupervised home environment.

Delayed insulin activity following subcutaneous injection is a barrier to attainment of glycaemic targets by any FCL system (22). Fiasp® is an ultra-rapid acting insulin preparation, containing insulin aspart and niacinamide. Compared to insulin aspart alone (NovoRapid®), subcutaneous injection of Fiasp® results in more rapid appearance of insulin in the intravascular space (23, 24). However, Fiasp® and NovoRapid® have only been directly

compared in AID users consuming meals without manual boluses in small short-term studies (25, 26).

The CLOSE IT trial assesses the efficacy of AAPS as FCL. The primary study objective is to evaluate TIR, comparing AAPS used as FCL to AAPS used as HCL during 12 weeks use. Secondary outcomes are the effectiveness of AAPS used as FCL relative to AAPS used as HCL with regards to glycaemic control and safety (27); psychosocial factors; platform performance; and user dietary factors. The CLOSE IT trial also includes a 4-week extension phase during which participants using FCL will change from NovoRapid® to Fiasp®, assessing changes in glycaemic metrics.

METHODS AND ANALYSIS

Study design

The CLOSE IT trial is an open label, multi-site, randomised, parallel-group 12-week non-inferiority trial evaluating the effectiveness and safety of AAPS used as FCL compared to AAPS used as HCL in adults (aged 18-70 years) with T1D.

All participants will complete a 12-week run-in phase, during which they become familiar with Dexcom G6® CGM and the Ypsomed insulin pump and initiate AAPS, used as HCL (see figure 1). Participants will then be randomly allocated (1:1) to one of two treatment groups:

A. Fully-automated closed loop system: Participants will continue to use AAPS, however will be advised not to bolus for meals, and not to correct high glucose levels unless they become symptomatic or sensor glucose levels are >15.0 mmol/L for ≥1 hour.

B. Hybrid closed loop system: Participants will continue to use AAPS as a hybrid closed loop system with manual mealtime boluses informed by carbohydrate counting, unchanged from therapy established during the run-in phase.

The RCT phase is 12 weeks duration, with the primary endpoint based on glycaemic data collected during the final 14 days.

Run-in phase

Following baseline assessments (Table 2), participants will be provided with an Ypsomed insulin pump, pump consumables, and unmasked Dexcom G6 CGM and trained in their use. Training will be customised for each individual to account for factors including prior familiarity with pump therapy and current glycaemia. NovoRapid® insulin will be exclusively used in the run-in and trial phases. A study dietitian will assess carbohydrate counting competency. Targeted education in carbohydrate counting will be provided if required.

Participants will receive an Android phone containing a locked version of the oref1 algorithm installed as an app (“Lotus”), effectively representing open-source AAPS. This system uses a heuristic algorithm that estimates a glycaemia projection every 5 minutes based on current glucose levels, insulin doses, announced carbohydrate consumption, and

user-specific parameters. When initially used, the system adjusts insulin dosing by modulating the basal rate. Users will subsequently activate “super micro boluses” (SMBs), which enable the system to deliver small, repeated boluses to correct high sensor glucose readings.

The run-in phase is 84 days, with day 1 defined as the day on which the study insulin pump is first used to deliver insulin to the participant. During this phase participants will commence HCL therapy using AAPS. Participants may either commence SAPT on day 1 and later transition to AID, or they may commence AID on day 1. AAPS settings will be optimised, including activation of SMBs. Participants will be supported through regular (at least weekly) electronic review of CGM data and pump settings by research staff. In-person study visits will be arranged as required.

Timing of AID commencement and optimisation of AAPS settings will be individualised for each participant; however, the target is for all participants to be established on AAPS with settings adjusted as best possible to optimise glycaemic control by day 70.

Trial phase

The trial phase is 84 days, representing days 85-168 of the trial. Participants will be informed of their allocated treatment group. Those allocated to HCL will continue to use AAPS in a similar manner to the run-in phase. Those allocated to FCL will be asked to discontinue any meal announcement and only give a manual bolus if specified criteria are met (sensor-detected glucose >15.0 mmol/L for ≥1 hour, or symptomatic hyperglycaemia).

As in the run-in phase, participants will be supported through regular (at least weekly) electronic review of CGM data and pump settings by research staff and in-person study visits as required. Documentation of all reviews will be maintained to demonstrate that participants in both groups have equal access to clinical support.

Extension phase

Participants allocated to FCL will, at completion of the trial phase, be sequentially invited to participate in the 28-day extension phase representing days 169-196 of the trial. Participants will change the insulin used in the study pump from NovoRapid® (insulin aspart) to Fiasp® (insulin aspart and niacinamide), while continuing to use AAPS as FCL under the same conditions as the trial phase. Participants will continue to be supported through regular (at least weekly) electronic review of CGM data and pump settings by research staff, and in-person study visits as required.

Patient involvement

People with T1D were involved in protocol design. AAPS, as an open-source system, has been developed and refined by people living with T1D. Individuals with T1D will also contribute to trial conduct and to reporting and dissemination of trial results.

Recruitment

The trial will enrol adults aged 18-70 with T1D at two sites: University of Otago, Christchurch (New Zealand) and the Baker Heart and Diabetes Institute, Melbourne (Australia). Recruitment commenced in April 2023 and is anticipated to be completed in 2024.

Study candidates will be identified by local clinicians. Formal recruitment will occur by research staff outside of routine clinical care, ensuring participants can provide informed consent free from undue influence. Evaluation of eligibility will be performed at screening according to inclusion and exclusion criteria (Table 1). To include a broad range of participants, these criteria allow for participants to be using either multiple daily insulin injections or insulin pump therapy at baseline, with no eligibility restrictions based on glycaemic metrics.

Sample size

The CLOSE IT trial has a non-inferiority design. Based on a mean TIR of 70% (SD 10%) approximating that seen in the HCL arm of the CREATE trial (20) and similarly designed trials of commercial HCL systems (3-7), and a largest clinically acceptable difference of 7% TIR, 70 participants (35 in each group) are required to provide 90% power at α=0.05. An overall sample size of 75 participants allows for five dropouts.

The pre-specified non-inferiority margin of 7% difference in TIR is larger than the 3% difference in TIR recommended in the 2023 international consensus statement on CGM metrics in clinical trials (27), which was published after development of this protocol. This does not preclude a finding of non-inferiority at a 3% margin. A secondary outcome is the proportion of participants in each trial arm for whom TIR does not decrease by >5%, consistent with the international consensus on a significant change in TIR for an individual.

A sample size of 20 participants in the extension phase will provide 80% power at two-sided α=0.05 to detect a mean within-person absolute change of 5%, assuming a within-person standard deviation of 7.5%.

Screening and enrolment

Individuals deemed a study candidate at pre-screening will be given the opportunity to review the participant information and consent form (PICF). Processes of obtaining informed consent will include the requirements of ISO 14155:2011 and Good Clinical Practice. All participants must sign and date the current ethics approved written informed consent form before any study specific assessments or procedures are performed. Additional consent will be sought for participation in interviews during the study as appropriate.

Table 2 delineates the baseline information which will be gathered post-consent, screening eligibility confirmation and enrolment in the study. Participants who do not usually use a Dexcom G6® CGM will be required to complete 14 days blinded CGM, with >75% sensor data capture. Participants who normally use a Dexcom G6® and who can provide CGM data from the preceding 14 days, will not be required to complete blinded CGM monitoring.

Randomisation

Participants will be randomly allocated (1:1) to receive FCL or HCL therapy. A computer-generated randomisation list, with permuted blocks of random size, will be pre-prepared by the study statistician, who will not be involved in participant enrolment or treatment allocation. The randomisation list will be concealed and loaded into the Research Electronic Data Capture (REDCap) database on Baker Institute servers.

Participants may only be randomised on day 85, following completion of the run-in phase. Then, research staff with authorisation to randomise participants may click the "randomise" button within REDCap which will assign the treatment to the study number and lock the fields containing the treatment group. This process will ensure allocation is concealed from research staff and participants until after run-in phase completion.

Primary outcome measures

The primary outcome is the percentage of time spent in target sensor glucose range (3.9-10.0 mmol/L) during the last 14 days of the trial phase, comparing FCL to HCL. Timing of all assessments is in Table 3.

Secondary outcome measures

Glycaemic control

HbA1c will be measured using a DCCT-aligned assay in local laboratories in venous blood from baseline and completion of the run-in and trial phases.

Individual CGM data will be pushed from the Android phone into a cloud-based server; Nightscout (described under Data Management). CGM data will be analysed according to standardised CGM metrics for clinical trials (27).

- Percentage of participants able to maintain TIR >70%
- Percentage of participants for whom TIR decreases by >5% between days 71-84 and days 155-168
- Time in tight range, defined as % CGM time 3.9-7.8 mmol/L
- % CGM time < 3.9 mmol/L
- % CGM time < 3.0 mmol/L
- % CGM time > 10.0 mmol/L
- % CGM time > 13.9 mmol/L
- Mean sensor glucose and glucose variability (expressed primarily as coefficient of variation and secondly as a standard deviation)
- Glycaemic outcomes differentiated as 24-hours, day (0600-2359 hours) and night (0000-0559 hours)

Insulin delivery systems: perceptions, ideas, reflections, and expectations (INSPIRE)

INSPIRE is a standardised tool with questions specific to AID systems, with demonstrated reliability of individual items on initial validation in a cohort of people with T1D (28). Participants will complete the 22-item adult baseline questionnaire during the study baseline assessment. Participants will complete the 22-item adult post-intervention questionnaire twice: at the end of the run-in phase (recognising that they will have used AID for most of this phase) and at the end of the trial phase.

Health status (EuroQol 5-dimensional questionnaire 5-level; EQ-5D-5L)

EQ-5D-5L is a generic patient-reported outcome questionnaire, with demonstrated validity and reliability in many disease areas (29). Although it does not provide information specific to AID use in T1D, as a widely used measure it can inform health economic analyses. EQ-5D-5L assesses overall health re: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Participants rate their health on a given day on each dimension with five levels of severity and give a global rating of their health overall on a 0-100 scale. Participants will complete the questionnaire three times: baseline, end of run-in, and end of trial phase.

System usability scale (SUS)

SUS, a validated global tool suited to consumer products to assess the user experience (30), comprises a 10-item questionnaire. Responses generate a score from 0-100, with a higher score representing greater user-friendliness. Participants will complete the questionnaire once, at the end of the trial phase.

Platform performance

Insulin delivery data will also be pushed from the Android phone into Nightscout and used to analyse platform performance and to verify participant adherence to their allocated treatment group (FCL or HCL).

- Percentage time using AID.
- Frequency of manual insulin boluses, further categorised in the FCL arm as boluses delivered in accordance with protocol and boluses delivered outside of protocol.
- Total insulin dose delivered by manual boluses, expressed as a percentage of overall total insulin dose, further categorised in the fully-automated arm as boluses delivered in accordance with protocol and boluses delivered outside of protocol.

User dietary factors

Participants will complete a 3-day diet record at study enrolment, between days 71-84 (run-in phase), between days 155-168 (trial phase), and between days 183-196 (extension phase). Diet records will be completed in the Easy Diet Diary app (Xyris Software Ltd, Australia) on the participant's phone, with assistance provided as required by a study dietitian. Participants will record all food, drinks, and times consumed in the app by searching the food database, scanning barcodes, and taking photos.

Qualitative interviews

Up to 15 FCL group participants will be invited to a qualitative interview at completion of the trial phase, exploring their experiences. Verbatim transcripts will undergo descriptive qualitative thematic analysis.

Tertiary outcome measures

Biobanking

Venous blood (plasma, serum and cell pellet) from participants in Australia will be stored (-80°C) for future testing at each time that HbA1c is tested. Analyses will relate to glycaemia (1,5 anhydroglucitol, glycated albumin), inflammation (CRP by high-sensitivity assay, vascular cell adhesion molecules), oxidative stress (myeloperoxidase, mitochondrial DNA copy number), and chronic complications (microRNAs).

Masking

Masking of participants and trialists is not possible due to the nature of the intervention, requiring participants to actively change the way in which they use the study devices.

Data analysis

A statistical analysis plan will be prepared by the study statistician and approved by principal investigators pre-analyses. Analysis will commence after the last participant has completed the RCT phase and will be use an up-to-date version of R, SAS, or Stata statistical software. CGM data, captured at 5-minute intervals throughout the study, will be used to calculate the primary endpoint (TIR) by dividing the number of CGM measures within the target glucose range (3.9 to 10.0 mmol/L) by the total number of CGM measures recorded. This primary, and all secondary CGM metrics, will be calculated for all participants during the last 14 days of the run-in phase (days 71-84) and the last 14 days of the RCT phase (days 155-168). Study outcomes will be descriptively summarised by study phase and treatment group.

The primary endpoint, and all continuous secondary CGM endpoints, will be compared between treatment groups during the last 14 days of the RCT phase using constrained longitudinal data analysis. This model adjusts for baseline levels by forcing treatment groups to share a common mean value. Study site will be included as a fixed effect, but no other variables will be adjusted for. This model will be used to estimate the intervention effect (between group difference) with 95% CI. Other continuous secondary endpoints, collected during clinic visits at the start and end of the RCT phase (e.g. HbA1c and psychosocial factors), will be analysed in an identical manner.

It is recognised that in non-inferiority trials, both intention-to-treat and per protocol analyses risk biases that favour finding non-inferiority; intention-to-treat analysis may suffer due to treatment non-adherence, and per protocol analysis due to confounding (31). The

primary analysis will be performed on the intent-to-treat population, and a per protocol analysis will also be performed and results considered when determining non-inferiority. For the per protocol analysis CGM metrics will be considered to belong to the FCL group on days where the participant has delivered no manual boluses outside of protocol conditions, or to the HCL group on days where the participant has delivered ≥2manual boluses outside of protocol conditions. Thus, a single participant may belong to different treatment groups on different days.

Extension study outcome measures and analysis

The extension study primary endpoint is TIR between days 183-196, calculated in a similar manner as above and compared to TIR during the last 14 days of the trial phase (days 155-168). The change in TIR after having changed from NovoRapid® to Fiasp® insulin will be calculated for each individual, and summarised for all 20 participants as mean and standard deviation with 95% CI. A paired t-test will be used to determine if the observed change is consistent with the null hypothesis of no change, with a two-sided $p<0.05$ used to determine statistical significance. Secondary metrics will be tested similarly, with the Benjamini and Hochberg method used to control false discovery rates associated with multiplicity of testing.

Data management

Data flow and management will occur through Nightscout, an open-source remote monitoring tool. Individual data will be pushed from the Android phone into Nightscout. Raw data, including all pump data at ≈5-minute intervals, will be uploaded de-identified to Nightscout. These data will then be downloaded onto secure servers at the Baker Institute and University of Otago. Nightscout accounts are de-identified to protect privacy and will only hold insulin pump and CGM data.

Qualitative interviews will be transcribed using Otter, an online artificial intelligence transcription service (Los Altos, USA). Interview content will be stored on an Otter-hosted online server, security of which is maintained by Otter and includes two-factor authentication to access participant data. Interviews will not collect personal identifying data (e.g. name, address, employment information, health records, or financial information).

All other de-identified data, including demographic, auxological, clinical, diabetic, lifestyle and psychosocial questionnaires and AEs will be electronically stored on REDCap in secure Baker Institute servers. REDCap is a web-based application which supports data capture for research studies, providing validated data entry and audit trails for tracking data manipulation and export procedures, and custom modules for participant randomisation and scheduling data collection events.

Records containing identifying details of New Zealand-based participants will be securely stored at the University of Otago and accessed only by New Zealand study staff. Records containing identifying details of Australia-based participants will be securely stored at the Baker Institute. These records will be retained for at least 15 years.

SPIRIT reporting guidelines for a protocol of a clinical trial (32) have been used.

ETHICS AND DISSEMINATION

The trial is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12622001400752p) and has been approved by the Alfred Health Ethics Committee (615/22) Australia and New Zealand Health and Disability Ethics Committees (2022 FULL 13832). Investigators will ensure the study conducted is in full conformance with the requirements of ISO 14155: 2011, the principles of the "Declaration of Helsinki" and with the laws and regulations of Australia and New Zealand. It is the responsibility of the investigator, or their designee to obtain signed and dated informed consent from each participant prior to study participation and after adequate explanation of the aims, methods, objectives, and potential hazards of the study and opportunity to ask questions and consider answers. If a participant is unable to give informed consent then the principal investigator will assess if the participant meets eligibility criteria. Any subject who cannot n read or write English will be excluded as they would not be able to comply with study requirements. During the informed consent process, participants will be given the option to opt-in or opt-out of the extension phase, qualitative interview, and biobanking components of the trial.

At trial-end participants will return to their usual Healthcare Professional team. New Zealand-based participants will be eligible to apply for compensation from the New Zealand Accident Compensation Corporation (ACC) in the event of a study related injury or illness. In the very unlikely event that ACC declines cover, then the University of Otago's clinical trial insurance would apply. For Australia-based participants, the Baker Institute's clinical trial insurance will apply in event of study-related injury or illness.

Any of the following adverse events (AE) will be documented in a timely manner:

1. Adverse Device Effects (ADE): adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device, and any event resulting from use error from intentional misuse of the investigational device.
2. Serious Adverse Events (SAE): adverse events resulting in death, life-threatening illness or injury, causing permanent impairment of body structure or function, requiring hospitalisation, or medical or surgical intervention to prevent any of the aforementioned SAEs.
3. Device Deficiencies (DD): any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

An electronic clinical record form (eCRF) will record:

- Start and stop date of the event
- A description of the event, including associated symptoms
- Assessment of seriousness
- Assessment of intensity

- Assessment of relationship to the investigational device
- Intervention/troubleshooting
- Outcome

All reportable AE will be followed up, if possible, until return to baseline status or stability, and if this is not achieved an explanation will be recorded in the eCRF. An independent Data Monitoring Committee (DMC) will assess accumulated data to ensure trial integrity and safety.

Dissemination of study results will be via rigorous peer-reviewed publications, conferences and patient advocacy groups. Investigators envisage trial results can deliver real-world health benefit for the global T1D community. The study is designed to maximise publishable outputs, including the first RCT outcome data for a fully-automated closed loop system in an outpatient setting. To deliver real-world impact investigators will leverage their representation on local and international diabetes advisory groups, and advocate approval of the open-source algorithm by relevant health regulators.

AUTHOR CONTRIBUTIONS

TMW and DT wrote the manuscript. All authors reviewed the manuscript. TMW, EB, DB, YE, JW, MdB, AJJ and NDC wrote the original study protocol. CK and SM advised regarding conduct of dietary aspects of the protocol.

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COMPETING INTERESTS STATEMENT

TMW, DT, EB, YE, NN have nothing to disclose.
MdB declares receiving speaker fees from Medtronic, Dexcom, Boerhinger Ingelheim, research support from Dexcom, Medtronic, Novonordisk, Pfizer, SOOIL, and has served as advisory board membership for Dexcom. NDC declares speaker fees from Novo Nordisk, Lilly, Boehringer Ingelheim, Abbott and research support from Ypsomed, Novo Nordisk, Boehringer Ingelheim, Astra Zeneca, Novartis. JW declares research support from Dexcom and SOOIL. DB declares employment at Nascence Biomed (which provides the technical platform for the CLOSE IT trial) and serving on an editorial board for Ascensia.

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TABLES

Table 1: Inclusion and exclusion criteria for participation in "CLOSE IT"

Inclusion criteria	Exclusion criteria
• Type 1 diabetes as per the American Diabetes Association classification for >12 months prior to the screening visit. • Aged 18-70 years inclusive. • Willing and able to adhere to the study protocol.	• If female, is pregnant or plans to become pregnant while participating in the study. A positive pregnancy test at screening is exclusionary. • Use of non-insulin glucose lowering therapy within 3 months of study commencement. • Severe renal impairment (eGFR <30mL/min/1.73m^2). • Any documented active or suspected malignancy, except appropriately treated basal cell or squamous cell carcinoma of the skin or any "in situ" carcinoma. • Acute cardiovascular event (myocardial infarction, unstable angina, stroke) in the 3 months prior to study commencement. • Severe hypoglycaemia[a] or diabetic ketoacidosis in the 3 months prior to study commencement. • Consumption of a very low carbohydrate diet, defined as carbohydrate intake <40g per day.

	• Inability to use insulin pump and/or mobile phone. • Any comorbid medical or psychological factors that would, on assessment by the investigators, make the person unsuitable for the study. • A lack of English literacy that would, on assessment by the investigators, make the person unsuitable for the study. • Allergy to insulin NovoRapid®

[a]*Defined as coma or convulsion requiring assistance from others.*

Table 2: Baseline assessments

Demographic	• Ethnicity • Gender • Highest level of education attained
Auxological	• Height • Weight • Body mass index
Diabetic	• Prior or current use of CGM or flash glucose monitoring (>75% use) • Number of episodes of severe hypoglycaemia in the 12 months prior to baseline visit

	• Number of episodes of diabetic ketoacidosis in the 12 months prior to baseline visit • Mean total daily dose (TDD) of insulin over the previous 14 days • Mode of insulin delivery (i.e. multiple daily injections or insulin pump) • Clinical examination for lipohypertrophy that may impair absorption of subcutaneous insulin
Laboratory	• Venous blood sample obtained for HbA1c, full blood count, and serum creatinine
Clinical	• Known allergies • Concomitant medications • Adverse event check
Diet	• Assessment of current carbohydrate intake, recorded over a three-day period
Psychosocial	• EuroQol 5-dimensional Questionnaire 5-Level (EQ-5D-5L) • Insulin Dosing Systems: Perceptions, Ideas, Reflections, and Expectations (INSPIRE) (pre-intervention questionnaire)
Blinded CGM	• 14 days use of blinded Dexcom G6

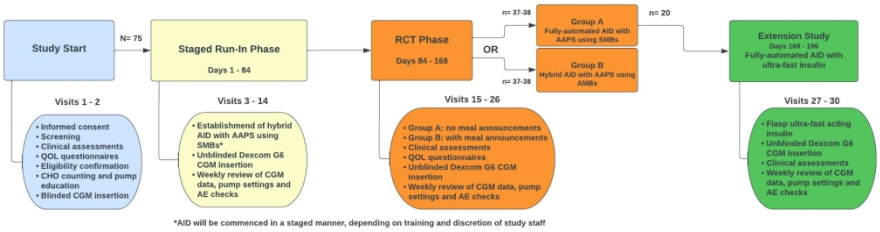
CGM = continuous glucose monitoring.

Table 3: Schedule of assessments

	Screening, consent, and baseline		Staged run-in phase (day 1-84) Establishment of hybrid AID with AAPS using SMBs	RCT phase (day 85-168) Group A: fully-automated AID with AAPS using SMBs Group B: hybrid AID with AAPS using SMBs			Extension study (n = 20) (day 169-196) Fully-automated AID with ultra-fast insulin	
		Day -14	Day 1-84	Day 85 ±4	Day 85-168	Day 168 ±4		Day 196 ±4
Screening and informed consent	X							
Demographics[a]	X							
Clinical assessment[b]	X			X		X		X
HbA1c	X			X		X		
1,5 anhydroglucitol and blood biomarkers for storage (Australia only)	x			x		x		x
Renal function and full blood count	X							
Height/weight	X			X		X		X
Pregnancy test[c]	X							
Carbohydrate counting education		X						
Dietary assessment[d]	X			X		X		X
Insulin pump training		X						
Blinded CGM[e]		X						
Randomisation				X				
INSPIRE and EQ-5D questionnaires	X			X[f]		X[f]		
SUS Questionnaire						X		
Qualitative interview[g]						X		
Weekly review of CGM data and pump settings			← →		← →		← →	
AE collection		← →						
Concomitant medication check	← →							

Pump and sensor glucose data		◄——►

[a]Age, gender, ethnicity, highest level of education, length of time with diabetes, usual mode of insulin delivery. [b]Includes review of current diabetes management. [c]Pregnancy test for females of childbearing potential only (all post-menarchal and pre-menopausal women). [d]Dietary assessment: daily carbohydrate intake during 3 separate days, recorded using Easy Diet Diary. [e]Blinded CGM: 14 days blinded CGM using Dexcom G6 system while continuing usual diabetes management. >75% blinded CGM capture is required before proceeding to run-in phase. [f]Post-intervention questionnaire. [g]Qualitative interview in up to 15 participants in the fully automated closed loop arm (Group A).



Study flow diagram

345x95mm (160 x 160 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	Available on request
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	13
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	13
Roles and responsibilities: sponsor and funder	#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	n/a

Roles and responsibilities: committees	#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)	Available on request
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	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	5
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, non-inferiority, exploratory)	5
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
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
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#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)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9-10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline,	8-10

		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	
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)	Table 3
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	7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
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	8

		separate document that is unavailable to those who enrol participants or assign interventions	
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	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#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 plan	#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	9-10

		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	
Data collection plan: retention	#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	10-11
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	11
Statistics: outcomes	#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	10-11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10-11
Statistics: analysis population and missing data	#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)	10-11

Methods: Monitoring			
Data monitoring: formal committee	#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	13
Data monitoring: interim analysis	#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	n/a
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	12-13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12

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)	Available on request
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	12
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	11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	No access planned outside of named authors

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	12
Dissemination policy: trial results	#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	13
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#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	Available on request
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	10

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BMJ Open

Study protocol for a randomised open label clinical trial examining the safety and efficacy of the Android Artificial Pancreas System (AAPS) with advanced bolus-free features in adults with type 1 diabetes: the 'CLOSE IT' (Closed Loop Open SourcE In Type 1 diabetes) trial

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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	DIABETES & ENDOCRINOLOGY, Clinical Trial, General diabetes < DIABETES & ENDOCRINOLOGY

Study protocol for a randomised open label clinical trial examining the safety and efficacy of the Android Artificial Pancreas System (AAPS) with advanced bolus-free features in adults with type 1 diabetes: the 'CLOSE IT' (Closed Loop Open SourcE In Type 1 diabetes) trial

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Keywords: Type 1 diabetes; closed loop; open-source; full automation

Word count: 4117

ABSTRACT

Introduction: Multiple automated insulin delivery (AID) systems have become commercially available following randomised controlled trials demonstrating benefit in people with type 1 diabetes (T1D). However, their real-world utility may be undermined by user-associated burdens, including the need to carbohydrate count and deliver manual insulin boluses. There is an important need for a "fully-automated closed loop" (FCL) AID system, without manual mealtime boluses. The (Closed Loop Open SourcE In Type 1 diabetes) CLOSE IT trial is a randomised trial comparing a FCL AID system to the same system used as hybrid closed loop (HCL) in people with T1D, in an outpatient setting over an extended timeframe.

Methods and analysis: Randomised, open-label, parallel, non-inferiority trial comparing the Android Artificial Pancreas System (AAPS) AID algorithm used as FCL to the same algorithm used as HCL. Seventy-five participants aged 18-70 will be randomised (1:1) to one of two treatment arms for 12 weeks: (a) FCL – participants will be advised not to bolus for meals; (b) HCL – participants will use the AAPS AID algorithm as HCL with announced meals. The primary outcome is the percentage of time in target sensor glucose range (3.9-10.0mmol/L) (TIR). Secondary outcomes include other glycaemic metrics, safety, psychosocial factors, platform performance, and user dietary factors. Twenty FCL arm participants will participate in a 4-week extension phase comparing glycaemic and dietary outcomes using NovoRapid® (insulin aspart) to Fiasp® (insulin aspart and niacinamide).

Ethics and dissemination: Approvals are by the Alfred Health Ethics Committee (615/22) (Australia) and Health and Disability Ethics Committees (2022 FULL 13832) (New Zealand). Each participant will provide written informed consent. Data protection and confidentiality will be ensured. Study results will be disseminated by publications, conferences and patient advocacy groups.

Trial registration number: ACTRN12622001400752 and ACTRN12622001401741.

ARTICLE SUMMARY

Strengths and limitations of this study

- CLOSE IT is a direct comparison of an automated insulin delivery (AID) system used as full closed loop (FCL) to that same system used as hybrid closed loop (HCL), in people with T1D during prolonged (12 weeks) outpatient follow-up.
- A 12-week run-in phase allows for optimisation of AID settings and pump self-management skills for all participants pre-randomisation.
- Dietary records and qualitative interviews will explore changes in dietary intake and attitudes in FCL system users.
- This trial is unmasked, with participants in both arms having access to the same devices, therefore there is a risk of spuriously concluding non-inferiority due to participant non-adherence.

INTRODUCTION

Type 1 diabetes (T1D) is a chronic health condition with substantial self-management demands regarding lifestyle, diet, and insulin dosing. Despite technological advances including continuous glucose monitoring (CGM) and insulin pump therapy, most people with T1D do not attain glycaemic targets (1), exposing them to risk of acute and chronic complications. Automated insulin delivery (AID) systems, also termed closed loop or artificial pancreas systems combine insulin pump technology, CGM, and control algorithms, to automatically adjust insulin delivery based on interstitial fluid glucose sensor readings (2). Multiple AID systems have become commercially available following large randomised controlled trials demonstrating improved glycaemia in people with T1D when compared to sensor-augmented pump therapy (SAPT) (3-7). Participants in these trials delivered manual insulin boluses pre-meals and real-world users are advised to do the same, hence these systems are termed “hybrid closed loop” (HCL).

Despite clear glycaemic benefits, real-world utility of AID systems may be undermined by the burden associated with their use. Notably, reluctance to start AID, and AID discontinuation once started, have been reported as more prevalent in users with suboptimal baseline glycaemia (8, 9). Reducing inequity in diabetes outcomes therefore requires minimisation of perceived and actual burdens of AID use. The burden is multifactorial, including device-related factors (10) and difficulty trusting automated insulin dosing decisions (10-14). However, the need to deliver manual insulin boluses with carbohydrate counting is likely to be contributory in many users. Observational T1D studies have described frequent missed mealtime boluses in pump-users (15, 16), and inaccuracies in carbohydrate counting (17, 18). There is therefore an important need for an AID system which can be used as “fully-automated closed loop” (FCL), without manual mealtime boluses.

The oref1 “reference design” algorithm introduced in OpenAPS (open-source artificial pancreas system) is also used in Android Artificial Pancreas System (AAPS) installed as an application on an Android phone. These “do-it-yourself” AID systems were first shared as open-source software in 2015 (19). The CREATE trial (n=97) found that those with T1D using oref1 for 24 weeks in an outpatient setting had higher mean time in range (TIR; percentage of CGM recordings between 3.9-10.0 mmol/L) compared to those using SAPT (71.2 vs. 54.5%, p<0.001) (20). Results broadly aligned with comparable trials of commercial AID systems (3-7). Furthermore, a pilot crossover trial comparing oref1 used as FCL to the same system used as HCL in adolescents with T1D during supervised 3-day periods found no significant difference in mean TIR (81 vs. 83%) (21). Further investigation is required to assess if these findings extrapolate to unselected patients in an unsupervised home environment.

Delayed insulin activity following subcutaneous injection is a barrier to attainment of glycaemic targets by any FCL system (22). Fiasp® is an ultra-rapid acting insulin preparation, containing insulin aspart and niacinamide. Compared to insulin aspart alone (NovoRapid®), subcutaneous injection of Fiasp® results in more rapid appearance of insulin in the intravascular space (23, 24). Fiasp® has shown modest improvements in TIR in trials of HCL systems (25, 26), and in a pivotal trial of the iLet Bionic Pancreas which uses “simplified meal

announcement" (27). Improved TIR has also been demonstrated with the ultra-rapid acting preparation Lyumjev® in HCL users (28). However, Fiasp® and NovoRapid® have only been directly compared in AID users consuming unannounced meals in small short-term studies (26, 29).

The CLOSE IT trial assesses the efficacy of AAPS as FCL. The primary study objective is to evaluate TIR, comparing AAPS used as FCL to AAPS used as HCL during 12 weeks use. Secondary outcomes are the effectiveness of AAPS used as FCL relative to AAPS used as HCL with regards to glycaemic control and safety (30); psychosocial factors; platform performance; and user dietary factors. The CLOSE IT trial also includes a 4-week extension phase during which participants using FCL will change from NovoRapid® to Fiasp®, assessing changes in glycaemic metrics.

METHODS AND ANALYSIS

Study design

The CLOSE IT trial is an open label, multi-site, randomised, parallel-group 12-week non-inferiority trial evaluating the effectiveness and safety of AAPS used as FCL compared to AAPS used as HCL in adults (aged 18-70 years) with T1D.

All participants will complete a 12-week run-in phase, during which they become familiar with Dexcom G6® CGM and the Ypsomed insulin pump and initiate AAPS, used as HCL (see figure 1). Participants will then be randomly allocated (1:1) to one of two treatment groups:

A. Fully-automated closed loop system: Participants will continue to use AAPS, however will be advised not to bolus for meals, and not to correct high glucose levels unless they become symptomatic or sensor glucose levels are >15.0 mmol/L for ≥1 hour.

B. Hybrid closed loop system: Participants will continue to use AAPS as a hybrid closed loop system with manual mealtime boluses informed by carbohydrate counting, unchanged from therapy established during the run-in phase.

The RCT phase is 12 weeks duration, with the primary endpoint based on glycaemic data collected during the final 14 days.

Run-in phase

Following baseline assessments (Table 1), participants will be provided with an Ypsomed insulin pump, pump consumables, and unmasked Dexcom G6 CGM and trained in their use. Training will be customised for each individual to account for factors including prior familiarity with pump therapy and current glycaemia. NovoRapid® insulin will be exclusively used in the run-in and trial phases. A study dietitian will assess carbohydrate counting competency. Targeted education in carbohydrate counting will be provided if required.

Participants will receive an Android phone containing a locked version of the oref1 algorithm installed as an app ("Lotus"), effectively representing open-source AAPS. This

system uses a heuristic algorithm that estimates a glycaemia projection every 5 minutes based on current glucose levels, insulin doses, announced carbohydrate consumption, and user-specific parameters. When initially used, the system adjusts insulin dosing by modulating the basal rate. In order to permit possible FCL use, participants will subsequently activate “super micro boluses” (SMBs), which enable the system to deliver small, repeated boluses to correct high sensor glucose readings, and an “unannounced meals” feature, which allows the algorithm to detect (and treat) glycaemic excursions that may represent unannounced carbohydrate intake.

The run-in phase is 84 days, with day 1 defined as the day on which the study insulin pump is first used to deliver insulin to the participant. During this phase participants will commence HCL therapy using AAPS. Participants may either commence SAPT on day 1 and later transition to AID, or they may commence AID on day 1. AAPS settings will be optimised, including activation of SMBs. Participants will be supported through regular (at least weekly) electronic review of CGM data and pump insulin delivery records by research staff. In-person study visits will be arranged as required. Table 2 summarises settings within oref1 that may be adjusted for each individual participant. Participants may choose to alternate between multiple profiles (each representing a combination of settings) and set temporary glucose targets, for example during exercise. While allowing a high degree of customisability, it is recognised that the large number of adjustable settings may add complexity. Adjustment of settings will be guided by regular meetings between research staff, sharing clinical and technical expertise.

Timing of AID commencement and optimisation of AAPS settings will be individualised for each participant; however, the target is for all participants to be established on AAPS with settings adjusted as best possible to optimise glycaemic control by day 70.

Trial phase

The trial phase is 84 days, representing days 85-168 of the trial. Participants will be informed of their allocated treatment group. Those allocated to HCL will continue to use AAPS in a similar manner to the run-in phase. Those allocated to FCL will be asked to discontinue any meal announcement and only give a manual bolus if specified criteria are met (sensor-detected glucose >15.0 mmol/L for ≥1 hour, or symptomatic hyperglycaemia).

Participants in both groups may continue to alternate between multiple profiles and take anticipatory measures prior to exercise, for example setting temporary glucose targets.

As in the run-in phase, participants will be supported through regular (at least weekly) electronic review of CGM data and pump insulin delivery records by research staff and in-person study visits as required. Further adjustments to oref1 settings may occur to optimise glycaemic control. Documentation of all reviews will be maintained to demonstrate that participants in both groups have equal access to clinical support.

Extension phase

Participants allocated to FCL will, at completion of the trial phase, be sequentially invited to participate in the 28-day extension phase representing days 169-196 of the trial. Participants will change the insulin used in the study pump from NovoRapid® (insulin aspart) to Fiasp® (insulin aspart and niacinamide), while continuing to use AAPS as FCL under the same conditions as the trial phase. Participants will continue to be supported through regular (at least weekly) electronic review of CGM data and pump settings by research staff, and in-person study visits as required.

Patient involvement

People with T1D were involved in protocol design. AAPS, as an open-source system, has been developed and refined by people living with T1D. Individuals with T1D will also contribute to trial conduct and to reporting and dissemination of trial results.

Recruitment

The trial will enrol adults aged 18-70 with T1D at two sites: University of Otago, Christchurch (New Zealand) and the Baker Heart and Diabetes Institute, Melbourne (Australia). Recruitment commenced in April 2023 and is anticipated to be completed in 2024.

Study candidates will be identified by local clinicians. Formal recruitment will occur by research staff outside of routine clinical care, ensuring participants can provide informed consent free from undue influence. Evaluation of eligibility will be performed at screening according to inclusion and exclusion criteria (Table 3). To include a broad range of participants, these criteria allow for participants to be using either multiple daily insulin injections or insulin pump therapy at baseline, with no eligibility restrictions based on glycaemic metrics.

Sample size

The CLOSE IT trial has a non-inferiority design. Based on a mean TIR of 70% (SD 10%) approximating that seen in the HCL arm of the CREATE trial (20) and similarly designed trials of commercial HCL systems (3-7), and a largest clinically acceptable difference of 7% TIR, 70 participants (35 in each group) are required to provide 90% power at α=0.05. An overall sample size of 75 participants allows for five dropouts.

The pre-specified non-inferiority margin of 7% difference in TIR is larger than the 3% difference in TIR recommended in the 2023 international consensus statement on CGM metrics in clinical trials (30), which was published after development of this protocol. This does not preclude a finding of non-inferiority at a 3% margin. A secondary outcome is the proportion of participants in each trial arm for whom TIR does not decrease by >5%, consistent with the international consensus on a significant change in TIR for an individual.

A sample size of 20 participants in the extension phase will provide 80% power at two-sided α=0.05 to detect a mean within-person absolute change of 5%, assuming a within-person standard deviation of 7.5%.

Screening and enrolment

Individuals deemed a study candidate at pre-screening will be given the opportunity to review the participant information and consent form (PICF). Processes of obtaining informed consent will include the requirements of ISO 14155:2011 and Good Clinical Practice. All participants must sign and date the current ethics approved written informed consent form before any study specific assessments or procedures are performed. Additional consent will be sought for participation in interviews during the study as appropriate.

Table 1 delineates the baseline information which will be gathered post-consent, screening eligibility confirmation and enrolment in the study. Participants who do not usually use a Dexcom G6® CGM will be required to complete 14 days blinded CGM, with >75% sensor data capture. Participants who normally use a Dexcom G6® and who can provide CGM data from the preceding 14 days, will not be required to complete blinded CGM monitoring.

Randomisation

Participants will be randomly allocated (1:1) to receive FCL or HCL therapy. A computer-generated randomisation list, with permuted blocks of random size, will be pre-prepared by the study statistician, who will not be involved in participant enrolment or treatment allocation. The randomisation list will be concealed and loaded into the Research Electronic Data Capture (REDCap) database on Baker Institute servers.

Participants may only be randomised on day 85, following completion of the run-in phase. Then, research staff with authorisation to randomise participants may click the “randomise” button within REDCap which will assign the treatment to the study number and lock the fields containing the treatment group. This process will ensure allocation is concealed from research staff and participants until after run-in phase completion.

Primary outcome measures

The primary outcome is the percentage of time spent in target sensor glucose range (3.9-10.0 mmol/L) during the last 14 days of the trial phase, comparing FCL to HCL. Timing of all assessments is in Table 4.

Secondary outcome measures

Glycaemic control

HbA1c will be measured using a DCCT-aligned assay in local laboratories in venous blood from baseline and completion of the run-in and trial phases.

Individual CGM data will be pushed from the Android phone into a cloud-based server; Nightscout (described under Data Management). CGM data will be analysed according to standardised CGM metrics for clinical trials (30).

- Percentage of participants able to maintain TIR >70%
- Percentage of participants for whom TIR decreases by >5% between days 71-84 and days 155-168
- Time in tight range, defined as % CGM time 3.9-7.8 mmol/L
- % CGM time < 3.9 mmol/L
- % CGM time < 3.0 mmol/L
- % CGM time > 10.0 mmol/L
- % CGM time > 13.9 mmol/L
- Mean sensor glucose and glucose variability (expressed primarily as coefficient of variation and secondly as a standard deviation)
- Glycaemic outcomes differentiated as 24-hours, day (0600-2359 hours) and night (0000-0559 hours)

Insulin delivery systems: perceptions, ideas, reflections, and expectations (INSPIRE)

INSPIRE is a standardised tool with questions specific to AID systems, with demonstrated reliability of individual items on initial validation in a cohort of people with T1D (31). Participants will complete the 22-item adult baseline questionnaire during the study baseline assessment. Participants will complete the 22-item adult post-intervention questionnaire twice: at the end of the run-in phase (recognising that they will have used AID for most of this phase) and at the end of the trial phase.

Health status (EuroQol 5-dimensional questionnaire 5-level; EQ-5D-5L)

EQ-5D-5L is a generic patient-reported outcome questionnaire, with demonstrated validity and reliability in many disease areas (32). Although it does not provide information specific to AID use in T1D, as a widely used measure it can inform health economic analyses. EQ-5D-5L assesses overall health re: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Participants rate their health on a given day on each dimension with five levels of severity and give a global rating of their health overall on a 0-100 scale. Participants will complete the questionnaire three times: baseline, end of run-in, and end of trial phase.

System usability scale (SUS)

SUS, a validated global tool suited to consumer products to assess the user experience (33), comprises a 10-item questionnaire. Responses generate a score from 0-100, with a higher score representing greater user-friendliness. Participants will complete the questionnaire once, at the end of the trial phase.

Platform performance

Insulin delivery data will also be pushed from the Android phone into Nightscout and used to analyse platform performance and to verify participant adherence to their allocated treatment group (FCL or HCL).

- Percentage time using AID.
- Frequency of manual insulin boluses, further categorised in the FCL arm as boluses delivered in accordance with protocol and boluses delivered outside of protocol.
- Total insulin dose delivered by manual boluses, expressed as a percentage of overall total insulin dose, further categorised in the fully-automated arm as boluses delivered in accordance with protocol and boluses delivered outside of protocol.

User dietary factors

Participants will complete a 3-day diet record at study enrolment, between days 71-84 (run-in phase), between days 155-168 (trial phase), and between days 183-196 (extension phase). Diet records will be completed in the Easy Diet Diary app (Xyris Software Ltd, Australia) on the participant's phone, with assistance provided as required by a study dietitian. Participants will record all food, drinks, and times consumed in the app by searching the food database, scanning barcodes, and taking photos.

Qualitative interviews

Up to 15 FCL group participants will be invited to a qualitative interview at completion of the trial phase, exploring their experiences. Verbatim transcripts will undergo descriptive qualitative thematic analysis.

Tertiary outcome measures

Biobanking

Venous blood (plasma, serum and cell pellet) from participants in Australia will be stored (-80°C) for future testing at each time that HbA1c is tested. Analyses will relate to glycaemia (1,5 anhydroglucitol, glycated albumin), inflammation (CRP by high-sensitivity assay, vascular cell adhesion molecules), oxidative stress (myeloperoxidase, mitochondrial DNA copy number), and chronic complications (microRNAs).

Masking

Masking of participants and trialists is not possible due to the nature of the intervention, requiring participants to actively change the way in which they use the study devices.

Data analysis

A statistical analysis plan will be prepared by the study statistician and approved by principal investigators pre-analyses. Analysis will commence after the last participant has completed the RCT phase and will be use an up-to-date version of R, SAS, or Stata statistical software. CGM data, captured at 5-minute intervals throughout the study, will be used to calculate the primary endpoint (TIR) by dividing the number of CGM measures within the target glucose range (3.9 to 10.0 mmol/L) by the total number of CGM measures recorded. This primary, and all secondary CGM metrics, will be calculated for all participants during the last 14 days of the run-in phase (days 71-84) and the last 14 days of the RCT phase (days 155-

168). Study outcomes will be descriptively summarised by study phase and treatment group.
The primary endpoint, and all continuous secondary CGM endpoints, will be compared between treatment groups during the last 14 days of the RCT phase using constrained longitudinal data analysis. This model adjusts for baseline levels by forcing treatment groups to share a common mean value. Study site will be included as a fixed effect, but no other variables will be adjusted for. This model will be used to estimate the intervention effect (between group difference) with 95% CI. Other continuous secondary endpoints, collected during clinic visits at the start and end of the RCT phase (e.g. HbA1c and psychosocial factors), will be analysed in an identical manner.

It is recognised that in non-inferiority trials, both intention-to-treat and per protocol analyses risk biases that favour finding non-inferiority; intention-to-treat analysis may suffer due to treatment non-adherence, and per protocol analysis due to confounding (34). The primary analysis will be performed on the intent-to-treat population, and a per protocol analysis will also be performed and results considered when determining non-inferiority. For the per protocol analysis CGM metrics will be considered to belong to the FCL group on days where the participant has delivered no manual boluses outside of protocol conditions, or to the HCL group on days where the participant has delivered ≥2manual boluses outside of protocol conditions. Thus, a single participant may belong to different treatment groups on different days.

Extension study outcome measures and analysis

The extension study primary endpoint is TIR between days 183-196, calculated in a similar manner as above and compared to TIR during the last 14 days of the trial phase (days 155-168). The change in TIR after having changed from NovoRapid® to Fiasp® insulin will be calculated for each individual, and summarised for all 20 participants as mean and standard deviation with 95% CI. A paired t-test will be used to determine if the observed change is consistent with the null hypothesis of no change, with a two-sided $p<0.05$ used to determine statistical significance. Secondary metrics will be tested similarly, with the Benjamini and Hochberg method used to control false discovery rates associated with multiplicity of testing.

Data management

Data flow and management will occur through Nightscout, an open-source remote monitoring tool. Individual data will be pushed from the Android phone into Nightscout. Raw data, including all pump data at ≈5-minute intervals, will be uploaded de-identified to Nightscout. These data will then be downloaded onto secure servers at the Baker Institute and University of Otago. Nightscout accounts are de-identified to protect privacy and will only hold insulin pump and CGM data.

Qualitative interviews will be transcribed using Otter, an online artificial intelligence transcription service (Los Altos, USA). Interview content will be stored on an Otter-hosted online server, security of which is maintained by Otter and includes two-factor authentication to access participant data. Interviews will not collect personal identifying

data (e.g. name, address, employment information, health records, or financial information).

All other de-identified data, including demographic, auxological, clinical, diabetic, lifestyle and psychosocial questionnaires and AEs will be electronically stored on REDCap in secure Baker Institute servers. REDCap is a web-based application which supports data capture for research studies, providing validated data entry and audit trails for tracking data manipulation and export procedures, and custom modules for participant randomisation and scheduling data collection events.

Records containing identifying details of New Zealand-based participants will be securely stored at the University of Otago and accessed only by New Zealand study staff. Records containing identifying details of Australia-based participants will be securely stored at the Baker Institute. These records will be retained for at least 15 years.
SPIRIT reporting guidelines for a protocol of a clinical trial (35) have been used.

ETHICS AND DISSEMINATION

The trial is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12622001400752 and ACTRN12622001401741) and has been approved by the Alfred Health Ethics Committee (615/22) Australia and New Zealand Health and Disability Ethics Committees (2022 FULL 13832). Investigators will ensure the study conducted is in full conformance with the requirements of ISO 14155: 2011, the principles of the "Declaration of Helsinki" and with the laws and regulations of Australia and New Zealand. It is the responsibility of the investigator, or their designee to obtain signed and dated informed consent from each participant prior to study participation and after adequate explanation of the aims, methods, objectives, and potential hazards of the study and opportunity to ask questions and consider answers. If a participant is unable to give informed consent then the principal investigator will assess if the participant meets eligibility criteria. Any subject who cannot n read or write English will be excluded as they would not be able to comply with study requirements. During the informed consent process, participants will be given the option to opt-in or opt-out of the extension phase, qualitative interview, and biobanking components of the trial.

At trial-end participants will return to their usual Healthcare Professional team. New Zealand-based participants will be eligible to apply for compensation from the New Zealand Accident Compensation Corporation (ACC) in the event of a study related injury or illness. In the very unlikely event that ACC declines cover, then the University of Otago's clinical trial insurance would apply. For Australia-based participants, the Baker Institute's clinical trial insurance will apply in event of study-related injury or illness.

Any of the following adverse events (AE) will be documented in a timely manner:

1. Adverse Device Effects (ADE): adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device, and any event resulting from use error from intentional misuse of the investigational device.

2. Serious Adverse Events (SAE): adverse events resulting in death, life-threatening illness or injury, causing permanent impairment of body structure or function, requiring hospitalisation, or medical or surgical intervention to prevent any of the aforementioned SAEs.
3. Device Deficiencies (DD): any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

An electronic clinical record form (eCRF) will record:

- Start and stop date of the event
- A description of the event, including associated symptoms
- Assessment of seriousness
- Assessment of intensity
- Assessment of relationship to the investigational device
- Intervention/troubleshooting
- Outcome

All reportable AE will be followed up, if possible, until return to baseline status or stability, and if this is not achieved an explanation will be recorded in the eCRF. An independent Data Monitoring Committee (DMC) will assess accumulated data to ensure trial integrity and safety.

Dissemination of study results will be via rigorous peer-reviewed publications, conferences and patient advocacy groups. Investigators envisage trial results can deliver real-world health benefit for the global T1D community. The study is designed to maximise publishable outputs, including the first RCT outcome data for a fully-automated closed loop system in an outpatient setting. To deliver real-world impact investigators will leverage their representation on local and international diabetes advisory groups, and advocate approval of the open-source algorithm by relevant health regulators.

AUTHOR CONTRIBUTIONS

TMW and DT wrote the manuscript. All authors reviewed the manuscript. TMW, EB, DB, YE, JW, MdB, AJJ, NN and NDC wrote the original study protocol. CK and SM advised regarding conduct of dietary aspects of the protocol.

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COMPETING INTERESTS STATEMENT

TMW, DT, EB, YE, NN have nothing to disclose.
MdB declares receiving speaker fees from Medtronic, Dexcom, Boerhinger Ingelheim, research support from Dexcom, Medtronic, Novonordisk, Pfizer, SOOIL, and has served as

advisory board membership for Dexcom. NDC declares speaker fees from Novo Nordisk, Lilly, Boehringer Ingelheim, Abbott and research support from Ypsomed, Novo Nordisk, Boehringer Ingelheim, Astra Zeneca, Novartis. JW declares research support from Dexcom and SOOIL. DB declares employment at Nascence Biomed (which provides the technical platform for the CLOSE IT trial) and serving on an editorial board for Ascensia.

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TABLES

Table 1: Baseline assessments

Demographic	• Ethnicity • Gender • Highest level of education attained
Auxological	• Height • Weight • Body mass index
Diabetic	• Prior or current use of CGM or flash glucose monitoring (>75% use) • Number of episodes of severe hypoglycaemia in the 12 months prior to baseline visit • Number of episodes of diabetic ketoacidosis in the 12 months prior to baseline visit • Mean total daily dose (TDD) of insulin over the previous 14 days • Mode of insulin delivery (i.e. multiple daily injections or insulin pump) • Clinical examination for lipohypertrophy that may impair absorption of subcutaneous insulin
Laboratory	• Venous blood sample obtained for HbA1c, full blood count, and serum creatinine
Clinical	• Known allergies

	• Concomitant medications • Adverse event check
Diet	• Assessment of current carbohydrate intake, recorded over a three-day period
Psychosocial	• EuroQol 5-dimensional Questionnaire 5-Level (EQ-5D-5L) • Insulin Dosing Systems: Perceptions, Ideas, Reflections, and Expectations (INSPIRE) (pre-intervention questionnaire)
Blinded CGM	• 14 days use of blinded Dexcom G6

CGM = continuous glucose monitoring.

Table 2: oref1 settings

Core settings	• Basal insulin rate • Insulin to carbohydrate ratio • Insulin sensitivity factor • Maximum insulin on board • Maximum bolus • Maximum basal rate
Super micro boluses (SMBs)	• Enable SMBs • Maximum minutes of basal to form SMBs
Common settings	• Basal rate multiplier safety ratios • Target blood glucose • Default temporary targets (e.g. for exercise) • Enable unannounced meals (UAM)
Insulin pharmacokinetic modelling	• Duration of insulin action • Time to peak insulin action
Other settings	• Default carbohydrate absorption rate

Table 3: Inclusion and exclusion criteria for participation in "CLOSE IT"

Inclusion criteria	Exclusion criteria
• Type 1 diabetes as per the American Diabetes Association classification for >12 months prior to the screening visit. • Aged 18-70 years inclusive. • Willing and able to adhere to the study protocol.	• If female, is pregnant or plans to become pregnant while participating in the study. A positive pregnancy test at screening is exclusionary. • Use of non-insulin glucose lowering therapy within 3 months of study commencement. • Severe renal impairment (eGFR <30mL/min/1.73m^2). • Any documented active or suspected malignancy, except appropriately treated basal cell or squamous cell carcinoma of the skin or any "in situ" carcinoma. • Acute cardiovascular event (myocardial infarction, unstable angina, stroke) in the 3 months prior to study commencement. • Severe hypoglycaemia[a] or diabetic ketoacidosis in the 3 months prior to study commencement. • Consumption of a very low carbohydrate diet, defined as carbohydrate intake <40g per day. • Inability to use insulin pump and/or mobile phone.

	• Any comorbid medical or psychological factors that would, on assessment by the investigators, make the person unsuitable for the study. • A lack of English literacy that would, on assessment by the investigators, make the person unsuitable for the study. • Allergy to insulin NovoRapid®

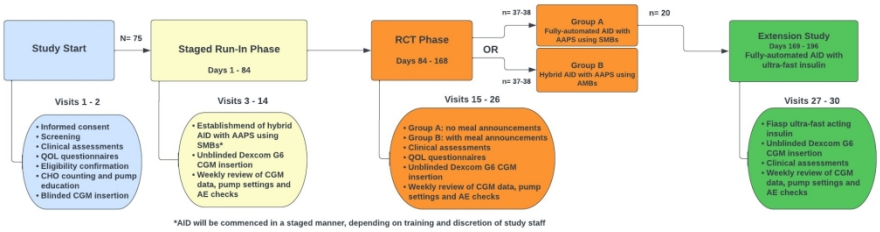
[a]*Defined as coma or convulsion requiring assistance from others.*

Table 4: Schedule of assessments

	Screening, consent, and baseline		Staged run-in phase (day 1-84) Establishment of hybrid AID with AAPS using SMBs	RCT phase (day 85-168) Group A: fully-automated AID with AAPS using SMBs Group B: hybrid AID with AAPS using SMBs			Extension study (n = 20) (day 169-196) Fully-automated AID with ultra-fast insulin	
		Day -14	Day 1-84	Day 85 ±4	Day 85-168	Day 168 ±4		Day 196 ±4
Screening and informed consent	X							
Demographics[a]	X							
Clinical assessment[b]	X			X		X		X
HbA1c	X			X		X		
1,5 anhydroglucitol and blood biomarkers for storage (Australia only)	x			x		x		x
Renal function and full blood count	X							
Height/weight	X			X		X		X
Pregnancy test[c]	X							
Carbohydrate counting education		X						
Dietary assessment[d]	X			X		X		X
Insulin pump training		X						
Blinded CGM[e]		X						
Randomisation				X				
INSPIRE and EQ-5D questionnaires	X			X[f]		X[f]		
SUS Questionnaire						X		
Qualitative interview[g]						X		
Weekly review of CGM data and pump settings			←		←		←	
AE collection		→						
Concomitant medication check	←							
Pump and sensor glucose data		→						

[a]Age, gender, ethnicity, highest level of education, length of time with diabetes, usual mode of insulin delivery. [b]Includes review of current diabetes management. [c]Pregnancy test for females of childbearing potential only (all post-menarchal and pre-menopausal women). [d]Dietary assessment: daily carbohydrate intake during 3 separate days, recorded using Easy Diet Diary. [e]Blinded CGM: 14 days blinded CGM using Dexcom G6 system while continuing usual diabetes management. >75% blinded CGM capture is required before proceeding to run-in phase. [f]Post-intervention questionnaire. [g]Qualitative interview in up to 15 participants in the fully automated closed loop arm (Group A).

Figure 1 caption: Study flow diagram



Study flow diagram

345x95mm (160 x 160 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	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	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	Available on request
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	13
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	13
Roles and responsibilities: sponsor and funder	#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	n/a

Roles and responsibilities: committees	#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)	Available on request
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	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	5
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, non-inferiority, exploratory)	5
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
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
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#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)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9-10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline,	8-10

		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	
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)	Table 3
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	7
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
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	8

		separate document that is unavailable to those who enrol participants or assign interventions	
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	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#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 plan	#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	9-10

		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	
Data collection plan: retention	#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	10-11
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	11
Statistics: outcomes	#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	10-11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10-11
Statistics: analysis population and missing data	#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)	10-11

Methods: Monitoring			
Data monitoring: formal committee	#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	13
Data monitoring: interim analysis	#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	n/a
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	12-13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12

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)	Available on request
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	12
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	11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	No access planned outside of named authors

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	12
Dissemination policy: trial results	#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	13
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#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	Available on request
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	10

https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai