WA HEALTH RESEARCH PROTOCOL

TEMPLATE FOR CLINICAL TRIALS

1 Trial Details

Protocol/Clinical Trial Title:	Redefining Glucose Thresholds for Hypoglycaemia Management in Children with Type 1 diabetes on Closed Loop Therapy: A Cross-over Clinical Trial		
Protocol Number (Version and Date):	V3 25.07.2024		
Amendment (Number and Date):			
Trial Start Date:	17.08.2024	**Trial Finish Date:**	17.02.2026
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Sponsor Name (if applicable):			
Laboratory Name (if applicable):			

Trial Summary

Hypoglycaemia is an inevitable and a common occurrence in Type 1 diabetes (T1D). Hypoglycaemia education is provided at the time of diagnosis and knowledge reviewed in the clinic as required. The current threshold for initiating hypoglycaemia treatment at glucose level < 3.9 mmol/L is on expert opinion, rather than evidence based. This level was chosen to avoid glucose levels from dropping even further (<3.0 mmol/L) which is considered as significant hypoglycaemia below which neurocognitive decline occurs. However, it needs to be appreciated that levels between 3.0 and 3.9 mmol/L are considered as normal in healthy individuals with no diabetes. With the availability of CGM and closed loop therapy as standard care in management of T1D, there is ability to support lower glucose thresholds for treatment as basal insulin delivery is suspended with prediction of hypoglycaemia. This will avoid overtreatment of hypoglycaemia and resultant high glucose levels.

The study aims at determining if reducing the cut-off of initiating treatment will be an acceptable hypoglycaemia threshold and will not be associated with an increase in time spent in hypoglycaemia <3.0 mmol/L with worsening of glycaemic outcomes.

This will be a single-centre, cross-over randomised controlled study in 40 participants, aged between 6 and 18 years on closed loop therapy. A two-treatment, two-period cross-over randomised controlled non-inferiority trial design will be used. Participants will be randomised to sequence A ('Standard Hypo Rx First'), or sequence B ('Revised Hypo Rx First'). 'Standard Hypo Rx First' participants will use the standard hypo treatment (i.e. Hypoglycaemia treatment initiated with glucose level <3.9 mmol/L) for 4 weeks (Period 1) after which they will switch to revised hypo treatment plan for 4 weeks (Hypoglycaemia treatment initiated at lower revised threshold of ≤ 3.6mmol/L) (Period 2).

There are no potential ethical issues in the proposed study.

2 Rationale / Background

Background summary

Type 1 diabetes (T1D) is a chronic health condition, predominantly diagnosed in children. The Department of Endocrinology and Diabetes at PCH is a state-wide diabetes service and caters to the health of approximately 1100 children and adolescents with T1D, with more than a hundred children diagnosed every year. The management of T1D requires life-long insulin replacement, either as subcutaneous injections or insulin pump. It is currently recommended that we aim for glucose levels between 3.9 and 10 mmol/L[1]. However, it needs to be appreciated that levels between 3.0 and 3.9 mmol/L can be considered as normal in healthy individuals with no diabetes.[2] International guidelines are for nations with varied resources and hence in Australia, with funded continuous glucose monitoring (CGM) devices with high CGM use and >50% on insulin pumps[3], there is ability to support tighter thresholds.

Hypoglycaemia is an invariable and inadvertent common occurrence with exogenous insulin therapy. It affects quality of life as both symptoms of hypoglycaemia and the treatment needed are disruptive in daily life[4]. Although it is unclear about how many episodes children experience on daily basis, most children experience at least one to two hypoglycaemic episodes in a week. There is no universally accepted numerical definition of hypoglycaemia. International guidelines recommend hypoglycaemia treatment to be initiated at <3.9 mmol/L (hypoglycaemia alert).[5] The alert was chosen based on the demonstration of onset of counter regulation below 3.9 mmol/L. However, concerns around the choice of this alert revolves around the small sample size (n=10) and the non-physiological methodology utilising the hyperinsulinemic hypoglycaemia clamp methodology in healthy adults with no diabetes[6] and the choice of this cut-off has been widely debated[7-9]. This level has been historically used for managing hypoglycaemia and studies supporting this cut-off are very limited. In the past, the incidence of severe hypoglycaemia was high, the accuracy of glucose monitoring devices was lower and there was a higher perceived fear of hypoglycaemia, both in families and health care professionals, advocating and accepting higher glucose targets. This level was chosen to avoid glucose levels from dropping even further (<3.0 mmol/L). Neurogenic symptoms and cognitive dysfunction occur below this level[6,10]. It is also known that glucose level <3.0 mmol/L may lead to defective hormonal counter regulation[11] and impaired awareness of hypoglycaemia with subsequent increased risk of severe hypoglycaemia[12]. These studies have informed the choice of <3.0 mmol/L as *clinically significant hypoglycaemia*.

Current improved diabetes care provides an opportunity to review the hypoglycaemia management. Advanced hybrid closed loop (AHCL) therapy is recommended therapy for all children with T1D[13]. These systems increase/decrease/suspend basal insulin delivery based on sensor glucose levels. (Almost 60% of our cohort in WA is on insulin pump therapy with 400 on AHCL). However, treatment of hypoglycaemia with closed loop therapy remains largely empirical and there is need for evidence-based guidelines. Standard hypoglycaemia management (glucose 15 g) with AHCL causes rebound hyperglycaemia[14]. This is because background insulin delivery is adjusted as per sensor glucose. The insulin delivery will be suspended with the prediction of hypoglycaemia and will recommence following an upward trend in sensor glucose, as directed by the closed loop algorithm. Hence, closed loop users are advised, albeit empirically, to reduce the amount of glucose (5 to 10 g) or to give approximately half the standard hypoglycaemia treatment[14,15]. To date, no studies have looked at the amount of glucose required or the treatment threshold to treat hypoglycaemia in children on AHCL.

Furthermore, there are families who elect to treat hypoglycaemia at lower glucose levels as they are more accepting of glucose levels between 3.5 and 3.9 mmol/L, contrary to the current education and guidelines (personal observation, self-reported by families in PCH clinic). A few centres nationally are also utilising the 3.5 mmol/L threshold[16,17]although there are no published data on hypoglycaemia rates from these centres. Families adopting lower thresholds either through personal experience or social media influence are left with no education or clinic support, and this has created confusion in the consumer/ community space. Use of CGM has also revealed high, above target glucose levels following hypoglycaemia treatments which further complicates insulin dosing and adds extra calories for the child. Besides, in clinical practice, we have not appreciated an increase in time <3.0 mmol/L when a lower cut-off of hypoglycaemia is used. Hence, there is a need to design studies which provide an evidence base that informs recommendations for treating hypoglycaemia for a child on AHCL living with diabetes.

This project is therefore novel, aimed at revisiting the cut-off of hypoglycaemia treatment. To summarise, there are no studies which have reviewed the appropriate threshold to initiate hypoglycaemia treatment although there has been debate around the cut-offs recommended for treatment[7]. This was largely due to the reliance on self-reported hypoglycaemia with patient-initiated blood glucose monitoring and fear of hypoglycaemia, making it difficult to design these studies. The availability of subsidised continuous glucose monitoring (CGM) devices which provide continuous real-time, 5-minutely glucose levels with alerts and trend arrows to the individual with T1D and the constant adjustment of insulin delivery with AHCL as per the sensor glucose provides the opportunity to answer this age-old question of which threshold is to be used for hypoglycaemia management.

We have received ethics for a study (RGS0000006153) which explores the real-life management strategies for hypoglycaemia management undertaken by the child with T1D and/or their caregivers. This study is a survey designed to be sent out to the entire clinic population and aims to provide insight into what families use as a threshold to initiate hypoglycaemia treatment and what works best for them. The revised cut-off will be guided by the results of study and discussion with clinical and research diabetes health care professionals from multidisciplinary team.

Consumer feedback for the study was sought in accordance with the Community Involvement Framework and Guidelines[18]. The information received has been incorporated into the study documentation.

Intervention

Interventional arm: Standard Hypo treatment on AHCL, instituted at a lower glucose level of ≤ 3.6 mmol/L This level was decided following consultation with the clinical and diabetes research teams, consumers and survey results from consumers from RGS0000006153.

Control arm: Standard Hypo treatment on AHCL, half of the treatment recommended with non-AHCL therapies[5].

(Non AHCL therapy: Approximately 0.3 g/kg glucose orally, which equates to 9 grams of glucose for a 30 kg child and 15 grams for children > 50 kg)

3 Trial Aims / Objectives / Hypotheses

RESEARCH QUESTIONS

Will lowering of hypoglycaemia alert from <3.9 mmol/L to a lower glucose level of 3.6 mmol/L increase time spent in clinically significant hypoglycaemia and/or worsen glycaemia in children and adolescents with T1D on advanced hybrid closed loop therapy (AHCL)?

AIMS

The study aims at determining if reducing the glucose level of initiating treatment will be an acceptable hypoglycaemia threshold and will not be associated with an increase in time spent in hypoglycaemia <3.0 mmol/L with worsening of glycaemic outcomes in children and adolescents with T1D on AHCL.

Hence, the primary aim of the study is

To determine whether hypoglycaemia treatment initiated at a lower glucose threshold is non-inferior to the standard glucose threshold of <3.9 mmol/L with regards to *time spent in clinically significant hypoglycaemia* (sensor glucose <3.0 mmol/L) in children and adolescents on AHCL.

Secondary aims are

1. To explore the impact of standard vs revised hypoglycaemia treatment on *glycaemic outcomes*: time spent in target glucose range of 3.9-10 mmol/L and time spent in hyperglycaemia > 10 mmol/L, > 13.9 mmol/L.
2. To determine whether hypoglycaemia treatment initiated at a lower glucose threshold is acceptable for the child with T1D and their families.

HYPOTHESIS

Time spent in clinically significant hypoglycaemia (< 3.0 mmol/L) will not be worse with revised hypoglycaemia threshold on closed loop therapy.

4 Trial Design

The scientific integrity of the trial and the credibility of the trial data depend substantially on the trial design and methodology.

Study Endpoints

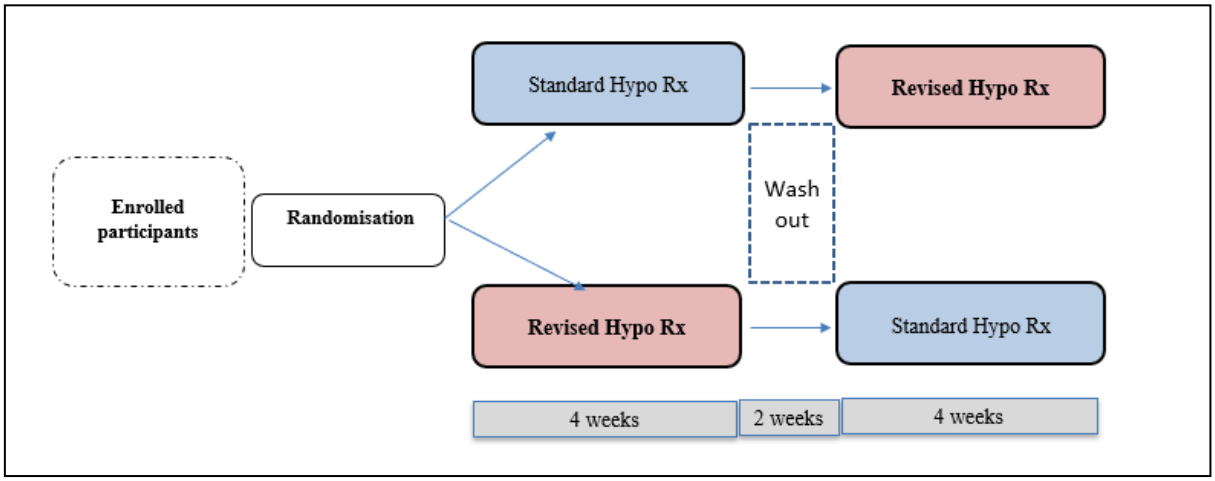
Primary outcome: Time spent in hypoglycaemia <3.0 mmol/L (Recommended to be <1%)[1]

Secondary outcomes:

1. CGM-derived Glycaemic metrics: Time in range 3.9-10 mmol/L (Recommended to be >70%), Time spent in hyperglycaemia >10 and >13.9 mmol/L (Recommended to be <25% and <5% respectively)[1]
2. Open-ended questions to determine participant's acceptability of revised hypoglycaemia cut-off.

Study Design

This will be a single-centre cross-over randomised controlled study. A two-treatment, two-period cross-over randomised controlled non-inferiority trial design will be used. Participants will be randomised to sequence A ('Standard Hypo Rx First'), or sequence B ('Revised Hypo Rx First'). Figure shows the study design.



'Standard Hypo Rx First' participants will use the standard hypo treatment[5] (i.e. Hypoglycaemia treatment initiated with glucose level <3.9 mmol/L) for 4 weeks (Period 1) after which they will switch to revised hypo treatment plan for 4 weeks (Hypoglycaemia treatment initiated at lower revised threshold of 3.6 mmol/L) (Period 2).

'Revised Hypo Rx First' participants will start with revised hypo treatment plan for 4 weeks (Period 1) and cross over to standard hypo Rx plan for 4 weeks (Period 2). The 4-week duration is chosen to capture adequate number of hypoglycaemic episodes. Most children are expected to experience at least 2 or more episodes per week.

There will be a wash-out phase of at least 2 weeks to prevent carryover effects.

VISIT 1 (F2F, 2hrs)

Eligibility Confirmation, Screening, Consent

Information sheets will be provided in advance to participants who potentially fit inclusion criteria.

Participants will be checked if they meet the inclusion criteria listed below in Section 5.2.

1. Gold score[12]

   Do you know when your hypos are starting?

Always Aware						Never Aware
1	2	3	4	5	6	7

   Self-reported, age >10 years. If child not able to self-report (parent proxy to be used)

2. Review of last 2 weeks of closed loop use and CGM metrics (from participants' pump and CGM report)

   Once deemed eligible, Consent signed by parent and investigator.

Data collection, Hypo education review and Randomisation Start of Period 1

All enrolled participants will have a review of hypoglycaemia education. Demographic, clinical and glycaemic data will be collected.

1. Auxology

   Height/Weight/BMI

2. Demographic

   Date of Birth/Gender/Ethnicity

3. Diabetes clinical

   a. Date of diagnosis

   b. Details of current therapy, total daily dose of insulin (mean of previous 7 days)

   c. CGM metrics: Time spent in hypoglycaemia, Time in range, Time in hyperglycaemia and glycaemic variability

   d. History of severe hypoglycaemia – coma or convulsion or episodes requiring third party assistance (events in last 12 months).

   e. History of diabetic ketoacidosis (DKA) in the last 12 months

   f. Hospital admissions in the last 12 months (DKA, Hyperglycaemia, Hypoglycaemia, Non- diabetes related)

   g. Co-morbidities and medications

   h. Hypoglycaemia awareness using Gold score[12]

4. Psychology measures: Psychological scales will be administered to the parents on an electronic platform . (Questionnaires are included in the appendix)

   a. Fear of hypoglycaemia: Hypoglycaemia fear survey Child and Parent[19]

5. Review Hypoglycaemia education.

6. Randomisation: Participants will be randomised to one of the two treatment sequences using https://sealedenvelope.com/ into a) Standard Hypo Rx First' or b) Revised Hypo Rx First'.

   The 4-week duration is chosen to capture adequate number of hypoglycaemic episodes. Most children are expected to experience at least 2 or more episodes per week.

   '*Standard Hypo Rx First'* participants will use the standard hypo treatment[5] (Hypoglycaemia treatment initiated with glucose level <3.9 mmol/L) for 4 weeks (Period 1)

   '*Revised Hypo Rx First'* participants will start with revised hypo treatment plan (Hypoglycaemia treatment initiated at a lower glucose level for 4 weeks (Period 1)

   During the study,

   1. All participants will be encouraged to continue to wear their CGM during the entire duration of the study and be on closed loop therapy. Basal insulin delivery is suspended with prediction of hypoglycaemia with closed loop therapy. Hence, if the participant is not on sensor, participants should take standard hypo Rx.

   2. Alerts

      2.1 Default (device in-built) urgent low alert at 3.0 mmol/L or 3.1 mmol/L will be **ON** for all participants during the study.

      2.2 Low alerts will be **ON**, in accordance with the glucose threshold of the study arm.

      2.3 Predictive low alerts are **optional**, as per choice of family.

   3. Revised Hypo Rx

      3.1 Always institute hypoglycaemia treatment when symptomatic (irrespective of blood/sensor glucose levels)

      3.2 Always institute hypoglycaemia treatment when the revised glucose threshold of 3.6 mmol/L is reached.

      3.3 Always institute hypoglycaemia treatment when sensor glucose < 3.9 mmol/L with downward trend arrows on CGM, there is active insulin on board (post meal-bolus) or during and post exercise/activity.

      3.4 Hypoglycaemia treatment should not be instituted when sensor glucose is between 3.7 and 3.9 mmol/L and stable glucose levels on CGM and in closed loop therapy.

   4. All participants will be advised to maintain a diary to log hypo events (glucose level, time and treatment given).

5. All participants will be provided an updated school management plan, when on the revised hypo Rx phase of the study,
6. During the entire study period, participants will be advised to ensure that they maintain optimal glucose levels as per recommendations for exercise and driving.

All participants will receive weekly review with email/phone calls by our team.

If time spent <3.0 mmol/L has doubled from baseline and/or is >1%, research staff (doctor and research diabetes educator) will review the participant to ensure 1) if they are 'true' hypoglycaemic events 2) explore the reason if 'true' hypoglycaemia.

Visit 2:

End of Period 1 (F2F / telehealth) (30min)

Participants will finish Period 1 and commence wash-out period for 2 weeks. In the wash-out period, hypo treatment will be treatment as usual (standard hypo treatment).

1. Diabetes clinical
    a. CGM metrics: Time spent in hypoglycaemia, Time in range, Time in hyperglycaemia and glycaemic variability
    b. Total daily dose of insulin (mean of previous 7 days)
2. Psychology measures:
    a. Fear of hypoglycaemia: Hypoglycaemia fear survey Child and Parent[19]
3. Any adverse events/severe adverse events

Visit 3:

Start of Period 2 (F2F / telehealth) (1 hour)

Standard Hypo Rx First' participants will switch to revised hypo treatment plan for 4 weeks.

'*Revised Hypo Rx First'* participants will switch to standard hypo Rx plan for 4 weeks.

All participants will receive weekly review with email/phone calls by our team. If time spent <3.0 mmol/L has doubled from baseline and/or is >1%, research staff (doctor and research diabetes educator) will review the participant to ensure 1) if they are 'true' hypoglycaemic events 2) explore the reason if 'true' hypoglycaemia.

Visit 4: End of Period 2/End of study (F2F / telehealth) (30 mins)

1. Diabetes clinical
    a. CGM metrics: Time spent in hypoglycaemia, Time in range, Time in hyperglycaemia and glycaemic variability
    b. History of severe hypoglycaemia – coma or convulsion or episodes requiring third party assistance (events in last 12 months).
    c. History of diabetic ketoacidosis (DKA) in the last 12 months
    d. Hospital admissions in the last 12 months (DKA, Hyperglycaemia, Hypoglycaemia, Non-diabetes related)
    e. Total daily dose of insulin (mean of previous 7 days)
    f. Co-morbidities and medications
2. Psychology measures:
    a. Fear of hypoglycaemia: Hypoglycaemia fear survey Child and Parent[19]
3. Any adverse events/severe adverse events
4. Open-ended questions to understand acceptability

Bias

To minimise selection bias, the population of all children eligible for the study will be identified from the Diabetes Database and invited by email and follow up telephone call.

Multiple avenues of recruitment will be utilised to try to reduce the influence of self-selection bias. For example, participants who meet the inclusion criteria will be emailed an invitation or could be approached in the diabetes outpatient clinics and informed about the study during their clinic visit. Recruitment via social media will also be utilised.

The unblinded nature of the participants and researchers is offset by the outcomes measured from the CGM glucose reports of the study participants.

There is a potential for participants to learn that the lower threshold may be beneficial and continue to use the revised threshold. However, all participants will be informed about the nature of the study design and encouraged to adhere to the specified thresholds of the study.

Blinding and Randomisation

This is an open-label study; study is not blinded

Device Tracking

Not applicable

Intervention/Product Description

Not applicable

Product Accountability Procedures

Not applicable

Trial Duration/Schedule

Each participant will be in the study for 10 weeks. Expected study duration to completion of visits is 18 months.

Trial Termination

Study participation is voluntary, and participants may withdraw at any time.

In general, once a participant is in the study, he/she will remain in the study unless the investigator believes it is not safe for the participant to continue. The criteria below will be used to determine safety:

1. *Severe hypoglycaemia* (seizure or coma or any episodes of hypoglycaemia with altered consciousness requiring glucagon).
2. *Non-adherence* to the protocol or development of a new medical condition or need for chronic use of a medication which in the judgment of the investigator increases risk for the participant.

Criteria for Suspending/Stopping Overall Study:

Criteria will be developed in conjunction with DSMB members at the first meeting.

The primary safety outcome will be severe hypoglycaemia defined objectively as coma/convulsion. The background rate of severe hypoglycaemia is low 3 per 100 patient years (2015) [20] and 2 per 100 patient years in the 2023 quarterly clinical review.

As severe hypoglycaemia events are experienced during the study, the DSMB will be notified in real-time. The DSMB will review if the event was caused due to the intervention.

At any time in the study, if two participants in the intervention arm have experienced severe hypoglycaemia resulting in coma or convulsion due to the intervention, the trial will be suspended. The DSMB will be called for an emergency review to discuss the early termination of the trial due to safety concerns.

The DSMB will notify the Principal Investigator and the Trial Management Group (TMG) if the study should be stopped. This will be conveyed to the ethics committee within 72h of the DSMB notification.

Data identification

The identification of any data to be recorded directly on the Case Report Forms (CRFs) (i.e. no prior written or electronic record of data), and to be considered to be source data.

5 Source and Selection of Participants

Source of Participants

This study aims to recruit children living with T1D and attending the Diabetes Clinic at PCH. Currently, there are approximately 1200 children and adolescents with diabetes, residing in Western Australia with 60% on insulin pump therapy and an increasing number of children on AHCL (n~400) as standard care.

Patients with T1D who satisfy the inclusion criteria, and consented to be contacted for research purposes, will be identified from the existing clinic database (Western Australian Children's Diabetes Database, WACDD) (HREC 2012051EP) by a Child and Adolescent Health Service employee and invited via email to partake in this study. Information on the study will also be disseminated via clinic newsletter and social media.

Participant inclusion criteria.

1. Diagnosis of Type 1 diabetes
2. 6 to 18 years
3. Duration of diabetes of >12 months (to ensure families have gained experience in managing hypoglycaemia)
4. On advanced closed loop therapy

   4.1 for at least 4 weeks and

   4.2 using the system optimally for >80% in last 2 weeks.

Participant exclusion criteria.

1. Impaired hypoglycaemia awareness. Self-reported Gold score ≥ 4 (these patients need higher glucose targets). For young children (age 6 to 10 years or if the child is developmentally young to self-report, parent-reported response will be used).
2. Increased time spent in hypoglycaemia as documented on CGM (>2% of time spent < 3.0 mmol/L and/or >6% of time spent < 3.9 mmol/L) for last two weeks
3. Families not willing to try lower cut-off due to fear of hypoglycaemia.
4. Severe hypoglycaemia (coma, convulsion or altered consciousness requiring third party assistance) in last 12 months.
5. Any medical or psychological disease state of the child and/or caregiver that limits capacity to participate in the study.

Participant withdrawal criteria

(a) when and how to withdraw participants from the investigational product/trial treatment;
Participants will be informed that they can withdraw from the study at any time. They can do so by contacting the research team.

(b) the type and timing of the data to be collected for withdrawn participant(s);
All data for withdrawn participant will be used for analysis.

(c) whether and how participants are to be replaced
Participants will not be replaced

(d) the follow-up for participants withdrawn from the investigational product/trial treatment.
If on the interventional arm, the participants will go back to standard care and will be followed up at their regular clinic visits.

6 Treatment of Participants

Description and justification for treatments, interventions or methods to be utilised

Revised Hypo Rx:

Product used is no different and is the glucose tablet or equivalent (available at pharmacies, multiple brands available) used by the participant for their standard hypoglycaemia management.

	Standard Hypo Rx	**Revised Hypo Rx**
Product name	Glucose tablet	Glucose tablet
Dose	0.15gm/kg glucose	0.15gm/kg
Route	Oral	Oral
Treatment instituted at	1. Glucose <3.9mmol/L 2. Symptomatic of hypo (Irrespective of glucose level)	1. Glucose ≤3.6mmol/L 2. Glucose < 3.9 mmol/L with downward trend arrows on CGM, there is active insulin on board (post meal-bolus) or during and post exercise/activity. 3. Symptomatic of hypo (Irrespective of glucose level)
Study period	4 weeks	4 weeks

Permitted medications/treatments

Participants will continue their usual insulin management on AHCL and medications for any associated comorbidities for the duration of the study.

Monitoring of participant compliance

During the 'Revised Hypo Rx' arm of the study, weekly contacts will be made by the research team to monitor adherence and hypoglycaemia events during the study.

7 Assessment of Efficacy

Outcomes

Percentage time spent in clinically significant hypoglycaemia (sensor glucose levels < 3.0 mmol/L)

Efficacy assessment

This is a non-inferior study design, and the assessment will be based on the time spent in hypoglycaemia (SG < 3.0 mmol/L). Time spent in hypo < 3.0 mmol/L in intervention as compared to control group will be calculated and the upper bound of 95% CI will be compared to a pre-defined non-inferiority limit.

8 Assessment of Safety

Risks and benefits

The revised hypo Rx has the potential to increase the time spent < 3.0 mmol/L (on CGM) and increase the number of hypo events. However, this risk is mitigated by:

1. Using only users of closed loop therapy in the study. Closed loop therapy will suspend basal insulin delivery with *prediction of hypo* and will only resume insulin delivery with rising sensor glucose (as directed by the closed loop algorithm).

2. Although the revised hypo treatment is to initiate treatment ≤ 3.6mmol/L, treatment of glucose level < 3.9 mmol/L is recommended if there are downward trend arrows on sensor, active insulin on board and precedent activity/exercise. All families are educated on decision making with CGM trend arrows around hyperglycaemia/hypoglycaemia management.

The benefits to the participants are that they may achieve better glycaemic control with a reduction in overtreatment with hypoglycaemia.

Safety

a. The sensor glucose levels of all study participants are available to participants in real-time which will enable them to take appropriate clinical action as required.

b. Urgent low notification at < 3.0 mmol/L or 3.1 mmol/L is default (factory-set) and will be 'on' for all participants at all times. Carers will also have this feature on their phone as part of remote monitoring.

c. Low notification will be set at 3.6mmol/L during the 'Revised Hypo Rx' phase and at <3.9 mmol/L for 'Standard Hypo Rx' phase.

d. AHCL is dependent on the sensor glucose levels and basal insulin delivery will be adjusted based on sensor glucose readings. It is therefore expected to mitigate any significant risk of hypoglycaemia < 3.0 mmol/L.

e. All participants are educated on the use of IM glucagon with severe hypoglycaemia (coma, convulsion, altered sensorium). This will be reviewed at Visit 1 as part of hypoglycaemia education.

f. Establishment of a Data and Safety Monitoring Board

g. All serious adverse events are to be recorded and reported to the investigators within 24hours.

Data and Safety Monitoring Board

A data and safety monitoring board (DSMB), consisting of an endocrinologist, a statistician and a clinical trial specialist, will be established to safeguard the interests of the trial participants and monitor the overall conduct of the study. The board will receive and review information on the progress and accruing data and provide advice on the conduct of the trial to the Principal Investigator and the Trial Management Group (TMG)*. The Principal Investigator and the TMG are required, under the DSMB charter for the study, to follow the DSMB's directions regarding the safety of the trial.

*The Trial Management Group, consisting of the research endocrinologist, the research nurse and the project manager, will be in charge of the day-to-day activities of the study.

Adverse event reporting

Adverse Event

1. Any undesirable clinical occurrence in a participant whether it is diabetes-related or not, that includes a clinical sign/symptom or condition.
2. Time spent in clinically significant hypoglycaemia < 3.0mmol/L is > 2%

Severe adverse events

1. Severe hypoglycaemia (seizure or coma or episodes requiring third party assistance)
2. Severe Diabetic ketoacidosis (venous ph <7.2)
3. Any diabetes-related in-patient admission
4. Results in death, is life-threatening

Follow-up of Adverse Events

The type of follow-up required after an adverse event will be determined by the doctor on the study team according to clinical need.

9 Data Management, Statistical Analysis and Record Keeping

Statistics and Interim Analysis

The primary analysis will assess the difference in time spent in clinically significant hypoglycaemia (<3.0 mmol/L) between the 'standard hypo Rx' and 'revised hypo Rx' conditions measured over four weeks. A linear mixed model including terms for treatment, period and sequence will be conducted on the log-transformation of 'time spent < 3.0 mmol/L'. The 'treatment' effect along with 95% confidence intervals will be produced. To demonstrate non-inferiority, the lower limit of the one-sided 95% confidence interval must fall below the pre-specified non-inferiority limit.

To reject the null hypothesis, and conclude non-inferiority of the intervention, the upper bound of the 95% confidence interval of the intervention effect must fall below the predefined non-inferiority limit of 0.56. This non-inferiority limit was identified based on discussions with clinicians and researchers as to what would represent a clinically relevant increase in hypoglycaemia.

Secondary outcomes will be analysed using a superiority approach. Mixed models including terms for treatment, period, and sequence will be used to estimate the effect of the intervention.

No corrections for multiple comparisons will be employed.

Sample Size

Real-world data from children on AHCL at our centre was recently evaluated. The median (IQR) time spent in hypoglycaemia <3.0 mmol/L was 0.2 (0.1-0.5)[21]. The distribution was approximately log normal with a mean(SD) of -1.3 (1.2). To inform the power calculation of this study, the paired difference in the log transformation of time < 3.0 mmol/L (%) in participants on closed loop therapy over the period of 12 weeks was reviewed. The distribution of the paired difference in the log-transformed '% time <3.0 mmol/L' was roughly normal with a standard deviation of 0.96.

A non-inferiority limit was identified based on discussions with clinicians and was set at a 75% increase in time spent in hypoglycaemia. This equates to a difference of 0.56 in the log-transformed time <3.0 mmol/L.

A sample of 36 participants would provide over 90% power for the boundary of a one-sided 97.5% confidence interval (one sided alpha of 0.025) to fall below the non-inferiority limit of 0.56. Allowing for 10% drop-out, we will recruit 40 participants.

Study Power and Significance

The primary analysis will have 90% power and a one-sided alpha of 0.025. For all secondary outcomes, alpha will be set at 0.05.

Statistical plan deviations

Any deviations to the original statistical plan will be reported to relevant ethics committees as an amendment to the scientific protocol and in the manuscript.

Selection of participants for analyses

All participants enrolled in the study will be included in the analysis.

Data management

Any information collected in connection with this project will remain confidential. Following consent, the participant will be provided with a unique study number which will be used on data collection instruments in place of identifying information to protect participant confidentiality.

All paper records will be stored in locked cabinets in the Endocrinology/diabetes office space on Level 2 at PCH. Electronic data will be stored on password protected CAHS REDCap database and the W:\Endocrinology\PMH\Endo Research\Departmental\study folder, which are accessible only by the study team.

On completion of the project, data analysis and publication of the project outcomes, the paper records will be archived as per PCH archiving policy. All records will be retained for 25y after publication of the study findings, after which they will be destroyed as per CAHS policies for research data management.

Procedures for missing, unused and spurious data:

Multiple imputation will be used to account for missing data in regression models.

10 Monitoring / Audit

Monitoring, Audit and Regulatory Inspections Statement

The trial investigators will permit trial-related monitoring, audits, and regulatory inspections, providing direct access to source data/documents

Procedures for monitoring and auditing

The study is monitored by the coordinating principal investigator monthly.

11 Quality Control and Quality Assurance

Compliance statement

The trial will be conducted in compliance with the protocol, Good Clinical Practice and the application regulatory requirements.

Quality control

All staff will be trained to ensure appropriate data collection in accordance with ICH-GCP guidelines. They will be trained on how to fill out the CRFs to ensure quality of data. Research nurse is an experienced diabetes educator with vast experience in clinical research trials.

12 Ethics

Participants are informed that their consent is voluntary and their participation in the trial or not will not affect their treatment in the clinic.

13 Budget, Financing, Indemnity and Insurance

This is an investigator-led project. All investigators and study personnel are indemnified by CAHS. Project cost covered by PCH Foundation.

14 Publication

The study will be registered at Australia New Zealand Clinical Trial Register (ANZCTR). Final results will be disseminated in a publication and presented at local and international conferences. All participants will be informed about the findings via newsletter and emails.

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16 Appendices

1. Fear of hypoglycaemia (parent, participant)
2. ISPAD Hypoglycaemia Management (2022 guidelines)
3. Questionnaire on Glucose Threshold for Hypoglycaemia

1. Fear of Hypoglycaemia

1.1 Parent version (for child < 12 years)

1.1.1 Behaviour scale

This survey is intended to find out more about how low blood sugar makes people feel and behave. Please answer the following questions as frankly as possible about how you felt during the past month.

Below is a list of things **parents** of children with diabetes sometimes DO IN ORDER TO AVOID LOW BLOOD SUGAR and related problems in their children.
Read each item carefully. Circle one of the numbers that best describes **YOU** during the past month.

0=NEVER	1=RARELY	2=SOMETIMES	3=OFTEN	4=ALMOST ALWAYS

1	Have my child eat large snacks at bedtime	0	1	2	3	4
2	Avoid having my child being alone when his/her sugar is likely to be low	0	1	2	3	4
3	Allow my child's blood sugar to be a little high to be on the safe side	0	1	2	3	4
4	Keep my child's sugar higher when he/she will be alone for awhile	0	1	2	3	4
5	Have my child eat something as soon as he/she feels the first sign of low blood sugar	0	1	2	3	4
6	Reduce my child's insulin when I think his/her sugar is too low	0	1	2	3	4
7	Keep my child's blood sugar higher when he/she plans to be away from me for awhile	0	1	2	3	4
8	Have my child carry fast-acting sugar	0	1	2	3	4
9	Have my child avoid a lot of exercise when I think his/her sugar is low	0	1	2	3	4
10	Check my child's sugar often when he/she plans to go on an outing	0	1	2	3	4
11	Get up in the middle of the night to check on my child or check my child's blood sugar levels	0	1	2	3	4

1.1.2 Worry scale

Worry: Below is a list of **concerns** parents of children with diabetes sometimes have.
Read each item carefully.
Circle one of the numbers that best describes
HOW OFTEN YOU WORRY ABOUT EACH ITEM

0=NEVER	1=RARELY	2=SOMETIMES	3=OFTEN	4=ALMOST ALWAYS

12	Child not recognizing/realizing that he/she is having a low	0	1	2	3	4
13	Child not having food, fruit, or juice with him/her	0	1	2	3	4
14	Child feeling dizzy or passing out in public	0	1	2	3	4
15	Child having a low while asleep	0	1	2	3	4
16	Child embarrassing self or friends/family in a social situation	0	1	2	3	4
17	Child having a low while alone	0	1	2	3	4
18	Child appearing to be “stupid” or clumsy	0	1	2	3	4
19	Child losing control of behavior due to low blood sugar	0	1	2	3	4
20	No one being around to help my child during a low	0	1	2	3	4
21	Child making a mistake or having an accident at school	0	1	2	3	4
22	Child getting a bad evaluation at school because of something that happens when his/her sugar is low	0	1	2	3	4
23	Child having seizures or convulsions	0	1	2	3	4
24	Child developing long term complications from frequent low blood sugar	0	1	2	3	4
25	Child feeling light-headed or faint	0	1	2	3	4
26	Child having a low	0	1	2	3	4
27	Rate how often you are confident in your ability to recognize your child’s low blood sugar	0	1	2	3	4
28	Rate how often you are confident in your ability to treat your child’s low blood sugar	0	1	2	3	4

1.2 Child version (for children > 12 years)

1.2.1 Behaviour scale

We want to find out more about what low blood sugar makes young people feel and do. Please answer the questions below as honestly as you can.

Below is a list of things young people with diabetes sometimes DO TO KEEP FROM HAVING LOW BLOOD SUGAR. Circle the number that best describes YOU.

	0=NEVER	1=RARELY	2=SOMETIMES	3=OFTEN	4=ALMOST ALWAYS
1	Eat large snacks at bedtime	0	1	2	3	4
2	Try not to be by myself when my sugar is likely to be low	0	1	2	3	4
3	Keep blood sugars a little high to be on the safe side	0	1	2	3	4
4	Keep blood sugar higher when I will be alone for a while	0	1	2	3	4
5	Eat something as soon as I feel the first sign of low blood sugar	0	1	2	3	4
6	Take less insulin when I think my blood sugar might get too low	0	1	2	3	4
7	Keep my blood sugar higher when I am going to be away from home	0	1	2	3	4
8	Carry some kind of sugar, drink, or food with me	0	1	2	3	4
9	Try not to do a lot of exercise when I think my sugar is low	0	1	2	3	4
10	Check my blood sugar often when I go away from home	0	1	2	3	4

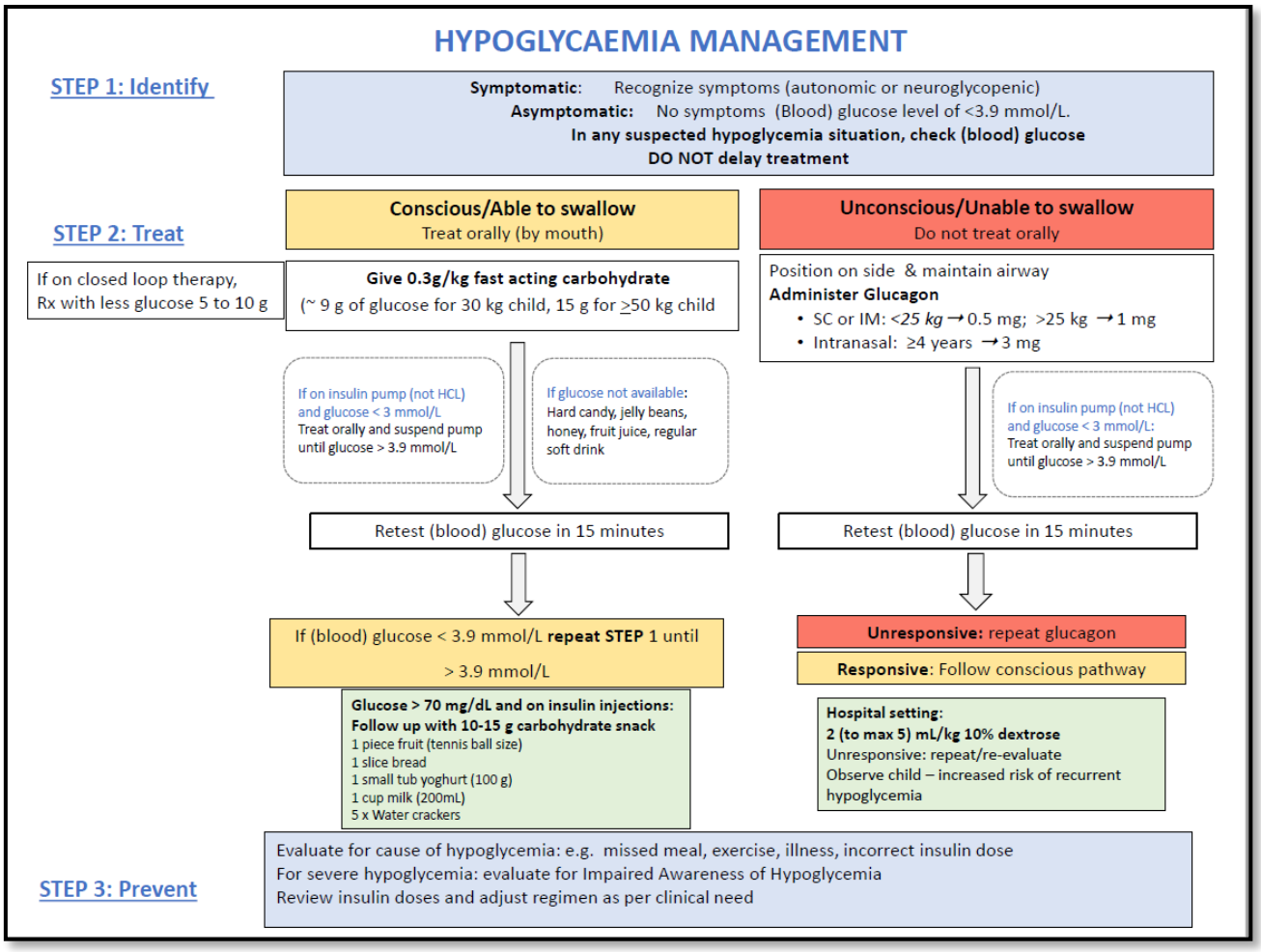
1.2.2 Worry scale

Below is a list of things that young people with diabetes sometimes worry about concerning low blood sugars.
Circle the number that best describes YOU

0=NEVER	1=RARELY	2=SOMETIMES	3=OFTEN	4=ALMOST ALWAYS

11	Not recognizing that my blood sugar is low	0	1	2	3	4
12	Not having food, fruit, or juice with me when my blood sugar gets low	0	1	2	3	4
13	Feeling dizzy or passing out in public because of low blood sugar	0	1	2	3	4
14	Having a reaction while asleep	0	1	2	3	4
15	Embarrassing myself because of low blood sugar	0	1	2	3	4
16	Having a reaction while I am by myself	0	1	2	3	4
17	Looking “stupid” or clumsy in front of other people	0	1	2	3	4
18	Losing control because of low blood sugar	0	1	2	3	4
19	No one being around to help me during a reaction	0	1	2	3	4
20	Making a mistake or having an accident at school	0	1	2	3	4
21	Getting in trouble at school because of something that happen when my sugar is low	0	1	2	3	4
22	Having seizures	0	1	2	3	4
23	Getting long term complications from low blood sugar	0	1	2	3	4
24	Feeling dizzy or woozy when my blood sugar is low	0	1	2	3	4
25	Having a low blood sugar	0	1	2	3	4

2. ISPAD Hypoglycaemia Management (2022 Guidelines)



3. Questionnaire on Glucose Threshold for Hypoglycaemia

Thank you for participating in the study.

1. Do you believe there is a need to change the current treatment recommendation to treat glucose level < 3.9 mmol/L? If yes, why? If no, why?

   _____

   _____

2. Do you think we should have one glucose level for hypo treatment for all or should we have this level personalised to the child/family?

   _____

   _____

3. On a scale of 1-5 where 1 = very easy and 5 = very hard:

Very easy	Easy	Neutral	Hard	Very hard
1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

How comfortable were you with treating hypo at a glucose level ≤ 3.6mmol/L mmol/L?

_____

_____

If you scored 3/4/5 (neutral/hard/very hard), can you elaborate?

_____

_____

_____

4. While treating hypo at a glucose level ≤ 3.6mmol/L, did you feel that you/your child spent more time below 3 mmol/L?

_____

_____

5. Were there any other situations, other than downward CGM arrows, post meal insulin bolus or exercise that you would do a hypo treatment for glucose < 3.9 mmol/L.

_____

_____

6. Any other comments?

_____

_____

_____