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# Safety and efficacy of the Predictive Low Glucose Management System in the prevention of hypoglycaemia: Protocol for randomised controlled home trial to evaluate the Suspend before Low function.

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**ABSTRACT:**

**Introduction**: Innovations with sensor-augmented pump therapy (SAPT) to reduce hypoglycaemia in patients with Type 1 diabetes are an ongoing area of research. The Predictive Low Glucose Management (PLGM) system incorporates continuous glucose sensor data into an algorithm and suspends basal insulin before the occurrence of hypoglycaemia. The system was evaluated in in-clinic studies and has informed the parameters of a larger home trial to study its efficacy and safety in real life.

**Methods and Analysis**: The aim of this report is to describe the study design and outcome measures for the trial. This is a six month, multicentre, randomised controlled home trial to test the PLGM system in children and adolescents with Type 1 diabetes. The system is available in the Medtronic MiniMed® 640G pump as the 'Suspend before low' feature. Following a run-in period, participants are randomised to either the control arm with SAPT alone or the intervention arm with SAPT and Suspend before low. The primary aim of this study is to evaluate the time spent hypoglycaemic (sensor glucose <3.5mmol/l) with and without the system. The secondary aims are to determine the number of hypoglycaemic events, the time spent hyperglycaemic and to evaluate safety with ketosis and changes in HbA1c. The study also aims to assess the changes in counter-regulatory hormone responses to hypoglycaemia evaluated by a hyperinsulinaemic hypoglycaemic clamp in a subgroup of patients with impaired awareness. Validated questionnaires are used to measure the fear of hypoglycaemia and the impact on the quality of life to assess the burden of disease.

**Ethics and Dissemination:** Ethics committee permissions were gained from respective Institutional Review boards. The findings of the study will provide high quality evidence to the ability of the system in the prevention of hypoglycaemia in real life.

**Trial registration**: Australia New Zealand Clinical Trials Registry ACTRN12614000510640

**Key words**: Predictive low glucose suspend, Suspend before low, Sensor-augmented pump therapy, Hypoglycaemia, Type 1 diabetes

**Strengths and limitations of this study**

- Strengths: This is the first randomised controlled home trial which will provide high quality evidence to the efficacy and safety of the PLGM system in the prevention of hypoglycaemia in real life situations. Apart from the glycaemic data, the six month duration of the study provides the ability to evaluate the impact of this technology on various psychosocial parameters in both children and their caregivers. The study will also determine the ability to use the system as a tool in restoration of hypoglycaemia awareness.
- Limitations: The settings for the Suspend before low feature are constant for the entire duration of the study; however these settings can be changed in real life. This study is a paediatric study and hence, one of the challenges will be in supporting and encouraging sensor use in the adolescent age group.

## INTRODUCTION

Hypoglycaemia imposes a considerable burden of disease on individuals and their families living with Type 1 diabetes.[1] Interventions designed to reduce and prevent hypoglycaemia are an important focus of research especially through the availability of sensor-augmented pump therapy (SAPT) and control algorithms. The Medtronic Low Glucose Suspend (LGS) system automatically suspends basal insulin delivery for up to two hours in response to sensor-detected hypoglycaemia thereby reducing the duration of hypoglycaemia.[2,3] This function has reduced the incidence of moderate and severe episodes of hypoglycaemia in patients with impaired awareness of hypoglycaemia (IAH)[4] and has been found to be safe with no rebound hyperglycaemia and ketosis.[5,6] While this system suspends insulin delivery when the patient is hypoglycaemic, the next step is to suspend insulin delivery before the patient is hypoglycaemic. The capacity to predict hypoglycaemia and suspend insulin delivery before hypoglycaemia occurs offers the additional advantage of preventing hypoglycaemia with further reduction in the actual time spent hypoglycaemic.

A significant proportion of children and adolescents with Type 1 diabetes have IAH with defective symptomatic and counter-regulatory hormone responses to hypoglycaemia. In a previous study by our group, IAH was reported by 29% of the clinic population.[7] Though loss of hypoglycaemia awareness may be reversed by meticulous avoidance of hypoglycaemia for three weeks,[8] this may be difficult to accomplish in real life and especially challenging in children. As predictive algorithms are designed to prevent hypoglycaemia, there may be an improvement in counter-regulatory hormones and return of adrenergic symptoms.

The initial in-clinic studies evaluating the predictive algorithms demonstrated a reduction in nocturnal and day-time hypoglycaemia induced by increased basal rates[9,10] and were subsequently evaluated on laptop based computers controlling insulin delivery used in pilot[11] and larger home trials.[12] In the era of rapidly evolving technology, various models have been used in the development of newer predictive algorithms. The Predictive Low Glucose Management System (PLGM) was evaluated in our centre under standardised in-clinic conditions in real life participants. The system was an investigational device and the predictive algorithm was incorporated in the BlackBerry® Storm smartphone which controlled the insulin infusion in participants on the Medtronic Paradigm Veo™ insulin pump

and Enlite™ glucose sensor with MiniLink™ REAL-Time transmitter. The system was tested with moderate-intensity exercise, excess subcutaneous insulin bolus and increased overnight basal rates which are common triggers of hypoglycaemia. With each hypoglycaemic stimulus, participants were randomised to a control arm with SAPT alone and an intervention arm with PLGM. The system suspended basal insulin when the sensor glucose was predicted to be 4.4mmol/l and found a reduction in the need for treatment of hypoglycaemia in all three settings in the intervention arm.[13] PLGM was also tested under in-clinic conditions in the PILGRIM study. There was reduction in hypoglycaemia with manual insulin bolus when administered to virtual patients and with real life patients when exercised.[14]

Guided by the results of the in-clinic studies, the home trial was designed to evaluate the efficacy of the PLGM system in free-living conditions. The PLGM system is available in the Medtronic MiniMed® 640G pump (Medtronic MiniMed, Northridge, CA) as the 'Suspend before low' feature which automatically suspends basal insulin infusion when hypoglycaemia is predicted. This system is evaluated in the home trial. In contrast to the PLGM in-clinic study, the home trial is of a longer duration, evaluates spontaneous rather than induced hypoglycaemia, and uses sensor glucose values rather than plasma glucose values to quantify hypoglycaemia.

We hypothesise that the PLGM system will reduce the time spent hypoglycaemic with time spent in hypoglycaemia reduced by at least 40% during six months of therapy with SAPT and Suspend before low vs. SAPT alone in patients with Type 1 diabetes. The system will also not result in an increase in hyperglycaemia or ketosis and will not result in a deterioration of glycaemic control as compared to standard SAPT. We further hypothesize that PLGM will improve hypoglycaemia awareness by reducing hypoglycaemia and will have a positive impact on the quality of life and reduce the fear of hypoglycaemia as determined by participant/parent questionnaires. Finally, the patient acceptability of the PLGM system will be no worse than their acceptability of standard SAPT.

## AIMS

The primary objective of the study is to compare the average percentage of time spent hypoglycaemic (sensor glucose level <3.5mmol/l) during six months of therapy with SAPT

and Suspend before low vs. SAPT alone. The secondary objectives are to compare events of hypoglycaemia, defined as 20 minutes or more with sensor glucose < 3.5mmol/l, during six months of therapy in both groups and to compare the average percentage of time spent hypoglycaemic (sensor glucose level <3.0mmol/l) and hyperglycaemic (sensor glucose level 10-15mmol/l and >15mmol/l). The study will also evaluate the time spent hypoglycaemic during day and night times. In addition, we aim to determine the safety of the system by determining the number of ketosis events (blood ketones >0.6mmol/l) and assess glycaemic control as measured by HbA1c at the end of six months. The study will also determine the counter-regulatory hormone responses to hypoglycaemia, evaluated during a hyperinsulinaemic hypoglycaemic clamp study, in a subgroup of participants with IAH. Hypoglycaemia awareness and the impact of diabetes on patient's quality of life, fear of hypoglycaemia, patient satisfaction and acceptability of the system will be evaluated using validated questionnaires administered at baseline, three months and end of the study. Here, we provide methodological details of the PLGM home trial.

## METHODS

This is a multicentre, unblinded, parallel, randomised controlled phase 3 home trial designed and conducted by five tertiary paediatric diabetes centres in Australia. The trial has been approved by Princess Margaret Hospital, Perth (HREC/2013121EP); The Children's Hospital at Westmead, Sydney (HREC/13/SCHN/405); John Hunter Children's Hospital, Newcastle (HREC/13/HNE/506); Royal Children's Hospital, Melbourne (HREC/13/HME/506); and Women's and Children's Hospital, Adelaide (HREC/13/WCHN/172). The trial is prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12614000510640). Children and adolescents with Type 1 diabetes on continuous insulin pump therapy (CSII) are approached through the diabetes clinics and are screened for eligibility in the study. Inclusion and exclusion criteria are summarised in Table 1.Written informed consent is obtained from participants aged ≥18 years and written parental consent and participant assent for those < 18 years. The study duration for each participant is six months from randomisation. The control group is expected to spend on average 5.79% of the time with glucose level <3.5mmol/L, with a standard deviation of 4.87%. 71 subjects would be required in each group to have 80% power to detect a decrease of 2.3% (40% reduction or effect size of 0.475) in time spent with glucose level <3.5mmol/L. It is anticipated that 175 participants would be recruited based on the estimated dropout rate of

20% to ensure a total of 142 participants for the duration of the trial with at least 71 participants in each arm. Recruitment will cease once this target is achieved. The study commenced in August 2014 and is currently ongoing.

**PLGM system**

The predictive algorithm is available in the commercially available Medtronic MiniMed® 640G pump (Medtronic MiniMed, Northridge, CA) designed for continuous subcutaneous insulin infusion (CSII) integrated with real-time continuous glucose monitoring (CGM). The system consists of the Medtronic MiniMed® 640G pump, CONTOUR NEXT LINK wireless blood glucose meter, Enlite™ glucose sensor and Guardian™ 2 Link transmitter. The transmitter sends the sensor glucose data wirelessly every five minutes to the pump and thereby provides real-time glucose measurements and trends. Calibration is required at least once every 12 hours. The pump is uploaded to transfer information to Medtronic CareLink® therapy Management Software through the use of CONTOUR NEXT LINK glucose meter which is also the uploading device.

'Suspend before low' is a SmartGuard function in the pump and suspends basal insulin infusion when sensor glucose is predicted to be below the set low limit in 30 minutes. The pump suspends basal insulin infusion when two criteria are met; the sensor glucose is at or within 3.9mmol/l (70mg/dl) above the set low limit and is predicted to be 1.1mmol/l (20mg/dl) above the set low limit in 30 minutes. The low limit is set for the entire study at 3.4mmol/l and the pump would therefore suspend insulin infusion when the sensor glucose is ≤7.3mmol/l (3.9+3.4) and predicted to be 4.5mmol/l (3.4+1.1) in 30 minutes. If the alert before low is on, the patient will receive an alert when insulin delivery is suspended. Once the pump is suspended, the insulin infusion will resume after a maximum suspend period of two hours or according to auto-resumption parameters if there is no patient interaction. Basal insulin will automatically resume if sensor glucose is above the low limit and trending upward and insulin has been suspended for at least 30 minutes. However, the infusion may be resumed earlier if the patient intervenes during the suspend time and overrides the suspend function. The auto-resumption feature was not present in LGS wherein the pump had a full two hour pump suspension in the absence of patient intervention and is novel to the predictive algorithm to reduce the potential of post suspend hyperglycaemia.

**Study Protocol:**

**VISITS 1 and 2: Training**

As shown in Figure 1, the first two visits are for training the participants; visit 1 for pump start and training and visit 2 for sensor training. Visits 1 and 2 are combined for participants previously competent with sensor use while in sensor naïve participants; visit 2 is undertaken at least four days after visit 1. During these visits, participants are also trained to upload the pump from home and are familiarised with sensor alerts and alarms. Sensor alerts and alarms are individualised for participants though every participant has the alert on low turned on at 3.4mmol/l. Questionnaires are administered to participants and/or their parents at this visit. These include Clarke's hypoglycaemia awareness questionnaire,[15] EQ-5D-Y and paediatric specific diabetes quality of life (PedsQL) questionnaires,[16] Hypoglycaemia Fear Survey,[17] and the Pump Satisfaction questionnaire.

**Run-in-period**

The two week run-in period is designed to establish competent use of the system and thereby identify subjects who are not likely to comply with the protocol. All participants are required to use CGM for >80% of the time during the run-in period and are to upload their pump for review by the investigators. Sensor naïve participants are provided an additional week of CGM use to warrant adequate training and familiarisation. The sensor data is reviewed prior to randomisation to ensure a cohort that has and is prone to hypoglycaemia. The participant should have one or more sensor values <3.5mmol/l at any time during the period of CGM use or one or more sensor values <4.4mmol/l on at least three different days. If the CGM is used successfully and the prerequisite criteria are met during the run-in period, participants return for visit 3.

**VISIT 3: Randomisation**

At this visit, measurement of HbA1c, height and weight are obtained and incidence of moderate and severe hypoglycaemia is recorded from the patient and medical records. Moderate hypoglycaemia is defined as any episode of hypoglycaemia during which the child/adolescent was lethargic, disoriented, confused and required third party assistance while severe hypoglycaemia is defined as an episode of loss of consciousness or seizure.[18] Minimisation of variation in gender, age, HbA1c and hypoglycaemia unawareness score is

undertaken at randomisation and performed using appropriate software (MinimPy).[19] Minimisation is a method of ensuring excellent balance between groups for known prognostic factors.[20] Participants are randomised to SAPT alone (control group) or SAPT and Suspend before low (intervention group). They are instructed on ketone testing; before breakfast and pre-bed in both groups and also at pump resumption after two hours of suspend in the intervention group during awake hours. They are also advised to test for ketones with glucose >15mmol/l or when unwell as part of routine diabetes care[21]. Participants are encouraged to upload their pump fortnightly and are provided with a home record log book to document hypoglycaemia, ketosis and sensor or pump related events.

**VISITS 4 and 5: Follow-up visits**

At the follow-up visits at three months (Visit 4) and six months (Visit 5), the diabetes educator/study nurse ensures that all information has been uploaded from the pump and ketone meter. A measurement of HbA1c, height and weight will be obtained along with record of moderate and severe hypoglycaemic episodes during this period. Participants and/or their parents' complete a quality of life questionnaire (EQ-5D-Y, PedsQL), Hypoglycaemia Fear Survey, Clarke's hypoglycaemia awareness questionnaire and the Pump Satisfaction Questionnaire during these visits.

**Hyperinsulinaemic Hypoglycaemic Clamps for participants with impaired hypoglycaemia awareness**

A score ≥4 on Clarke's questionnaire indicates IAH[15] and participants with IAH and above 12 years of age are eligible for hyperinsulinaemic hypoglycaemic clamp studies which will determine the counter-regulatory responses to hypoglycaemia. The studies will be performed at baseline and after six months, irrespective of whether the participant is in the control or intervention group. The clamp procedure will involve infusing insulin intravenously at a constant rate of 80mU/m$^2$ per minute and plasma glucose targets will be achieved by adjusting the rate of infusion of a solution of 20% glucose in water. Prior to induction of hypoglycaemia, plasma glucose will be maintained in euglycaemia (5-6mmol/l) for 60 minutes followed by gradual reduction over 30 minutes to a nadir of 2.8mmol/l. This controlled decline will be guided by plasma blood glucose measurements taken at 5-minute intervals. The blood glucose concentration of 2.8mmol/l will be maintained for 40 minutes before euglycaemia will be restored. For the duration of the clamp procedure, blood glucose will be measured using glucose oxidase technique with a bedside YSI analyser. Venous

blood will be sampled during the euglycaemic and hypoglycaemic phase to determine plasma insulin, glucagon, epinephrine, norepinephrine, cortisol, and growth hormone concentrations during both study days.

## MONITORING OF SAFETY AND ADVERSE EVENTS

Participants are advised to confirm all sensor alerts (on high, low and suspend) events with a capillary blood glucose. Ketone levels are monitored in both control and intervention groups and participants are advised to contact the on-call paediatric endocrinologist or paediatrician in the event of ketosis and/or being unwell. Ketone data are uploaded at the study visits 4 and 5. A data safety and monitoring board (DSMB) scrutinises conduct of the study team and reviews data arising from the study.

All adverse events defined as a clinical sign, symptom or condition that is causally related to the device implantation procedure, the presence of the device, or the performance of the device system will be recorded and evaluated by the local investigator. Serious adverse event is defined as one which is fatal or life threatening or requires hospitalization for diabetic ketoacidosis or severe hypoglycaemia. Adverse events and serious adverse events will be reported to the DSMB and the ethics at each centre for their review.

## STATISTICAL ANALYSIS

The analysis population will be the intention-to-treat population, which is defined as all patients who are randomised and have at least one visit after baseline. P-values <0.05 will be considered statistically significant and 2-sided P-values will be reported. The time spent hypoglycaemic or hyperglycaemic and the continuous outcome measures will be analysed using a likelihood-based, mixed-effects model repeated measures (MMRM) approach. Rates of hypoglycaemia as well as incidence of moderate and severe hypoglycaemia will be analysed as unadjusted incidence rates based on the Poisson distribution. Incidence rates and incidence rate differences will be presented with their associated 95% confidence intervals calculated as exact Poisson confidence limits. Number of ketosis events and other safety outcomes will be tabulated and presented as n and %. The counter-regulatory hormone response responses to hypoglycaemia measured during the hyperinsulinaemic hypoglycaemic clamp study in participants with IAH will be presented with descriptive statistics.

## DISCUSSION

This is the first multicentre randomised controlled home trial evaluating the performance of the 'Suspend before low' function in free-living conditions. Though the Medtronic MiniMed® 640G pump is commercially available, there are no studies as yet testing the efficacy of the system in real world. Apart from the glycaemic data, the safety of the system can be monitored with ketones in both treatment groups. In addition, the six month study duration will provide us the ability to evaluate the psychological outcomes specifically addressing quality of life and fear of hypoglycaemia in both patients and their care-givers. The clamp data will also inform us the counter-regulatory hormone responses in participants with IAH. An improvement in hormonal responses, if demonstrated, will enable us to use this this system as a tool in this high risk group to help restore awareness of hypoglycaemia.

SAPT with Suspend before low feature represents an important advancement in insulin delivery systems because of its potential in reduction of hypoglycaemia. This study will be the first to quantify these effects in a randomised controlled trial in patients with Type 1 diabetes who are predisposed to hypoglycaemia, and the results will provide a benchmark for further studies of automated insulin delivery systems.

**Contributors:** TJ, ED, GA, FC, BK and JF conceived the study design, and TL, NP, HR, MA and JN contributed to the conception of the design. MA drafted the manuscript, and all authors reviewed the draft of the manuscript. All authors approved the final manuscript to be published.

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**Competing Interests:** This is an investigator initiated trial. All authors declare that there are no competing interests.

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**Table 1:** Inclusion and Exclusion Criteria for PLGM home trial

| **Inclusion criteria** | **Exclusion criteria** |
|---|---|
| Age: 8 to 20 years | Medical conditions predisposing to hypoglycaemia other than diabetes |
| Duration of Type 1 diabetes ≥1 year | Oral glycaemic medications e.g. metformin, sulphonylureas |
| On CSII ≥ 6 months | Inability or refusal to meet protocol requirements |
| HbA1c at eligibility <10% (86mmol/mol) | Pregnancy |

**Figure 1**: Study visits

Flow diagram represents the visits of the study.

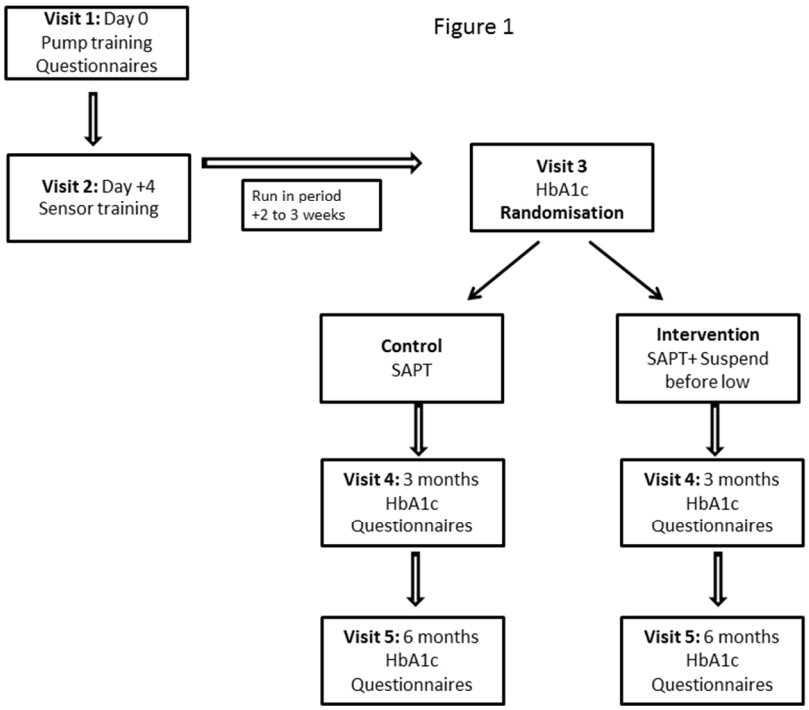


Figure 1

Flow diagram represents the visits of the study.
254x190mm (96 x 96 DPI)

# CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | 1 |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 2 |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | 3,4,5 |
| | 2b | Specific objectives or hypotheses | 5 |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | 6 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | - |
| Participants | 4a | Eligibility criteria for participants | 6,13 |
| | 4b | Settings and locations where the data were collected | 6 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 6,7 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 6 |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | - |
| Sample size | 7a | How sample size was determined | 6 |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | - |
| Randomisation: | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | 8 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 8 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | - |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | - |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those | - |

| | | | |
|---|---|---|---|
| | | assessing outcomes) and how- | |
| | 11b | If relevant, description of the similarity of interventions | - |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | 9,10 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | 10 |
| **Results** | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | |
| | 14b | Why the trial ended or was stopped | |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) | |
| **Discussion** | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | |
| **Other information** | | | |
| Registration | 23 | Registration number and name of trial registry | 2 |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | Manuscript is protocol paper |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders | 11 |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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# Safety and efficacy of the Predictive Low Glucose Management System in the prevention of hypoglycaemia: Protocol for randomised controlled home trial to evaluate the Suspend before Low function.



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# Safety and efficacy of the Predictive Low Glucose Management System in the prevention of hypoglycaemia: Protocol for randomised controlled home trial to evaluate the Suspend before Low function.

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**ABSTRACT:**

**Introduction**: Innovations with sensor-augmented pump therapy (SAPT) to reduce hypoglycaemia in patients with Type 1 diabetes are an ongoing area of research. The Predictive Low Glucose Management (PLGM) system incorporates continuous glucose sensor data into an algorithm and suspends basal insulin before the occurrence of hypoglycaemia. The system was evaluated in in-clinic studies and has informed the parameters of a larger home trial to study its efficacy and safety in real life.

**Methods and Analysis**: The aim of this report is to describe the study design and outcome measures for the trial. This is a six month, multicentre, randomised controlled home trial to test the PLGM system in children and adolescents with Type 1 diabetes. The system is available in the Medtronic MiniMed® 640G pump as the 'Suspend before low' feature. Following a run-in period, participants are randomised to either the control arm with SAPT alone or the intervention arm with SAPT and Suspend before low. The primary aim of this study is to evaluate the time spent hypoglycaemic (sensor glucose <3.5mmol/l) with and without the system. The secondary aims are to determine the number of hypoglycaemic events, the time spent hyperglycaemic and to evaluate safety with ketosis and changes in HbA1c. The study also aims to assess the changes in counter-regulatory hormone responses to hypoglycaemia evaluated by a hyperinsulinaemic hypoglycaemic clamp in a subgroup of patients with impaired awareness. Validated questionnaires are used to measure the fear of hypoglycaemia and the impact on the quality of life to assess the burden of disease.

**Ethics and Dissemination:** Ethics committee permissions were gained from respective Institutional Review boards. The findings of the study will provide high quality evidence to the ability of the system in the prevention of hypoglycaemia in real life.

**Trial registration**: Australia New Zealand Clinical Trials Registry ACTRN12614000510640

**Key words**: Predictive low glucose suspend, Suspend before low, Sensor-augmented pump therapy, Hypoglycaemia, Type 1 diabetes

## Strengths and limitations of this study

- Strengths: This is the first randomised controlled home trial which will provide high quality evidence to the efficacy and safety of the PLGM system in the prevention of hypoglycaemia in real life situations. Apart from the glycaemic data, the six month duration of the study provides the ability to evaluate the impact of this technology on various psychosocial parameters in both children and their caregivers. The study will also determine the ability to use the system as a tool in restoration of hypoglycaemia awareness.
- Limitations: The settings for the Suspend before low feature are constant for the entire duration of the study; however these settings can be changed in real life. This study is a paediatric study and hence, one of the challenges will be in supporting and encouraging sensor use in the adolescent age group.

## INTRODUCTION

Hypoglycaemia imposes a considerable burden of disease on individuals and their families living with Type 1 diabetes.[1] Interventions designed to reduce and prevent hypoglycaemia are an important focus of research especially through the availability of sensor-augmented pump therapy (SAPT) and control algorithms. The Medtronic Low Glucose Suspend (LGS) system automatically suspends basal insulin delivery for up to two hours in response to sensor-detected hypoglycaemia thereby reducing the duration of hypoglycaemia.[2,3] This function has reduced the incidence of moderate and severe episodes of hypoglycaemia in patients with impaired awareness of hypoglycaemia (IAH)[4] and has been found to be safe with no rebound hyperglycaemia and ketosis.[5,6] While this system suspends insulin delivery when the patient is hypoglycaemic, the next step is to suspend insulin delivery before the patient is hypoglycaemic. The capacity to predict hypoglycaemia and suspend insulin delivery before hypoglycaemia occurs offers the additional advantage of preventing hypoglycaemia with further reduction in the actual time spent hypoglycaemic.

A significant proportion of children and adolescents with Type 1 diabetes have IAH with defective symptomatic and counter-regulatory hormone responses to hypoglycaemia. In a previous study by our group, IAH was reported by 29% of the clinic population.[7] Though loss of hypoglycaemia awareness may be reversed by meticulous avoidance of hypoglycaemia for three weeks,[8] this may be difficult to accomplish in real life and especially challenging in children. As predictive algorithms are designed to prevent hypoglycaemia, there may be an improvement in counter-regulatory hormones and return of adrenergic symptoms.

The initial in-clinic studies evaluating the predictive algorithms demonstrated a reduction in nocturnal and day-time hypoglycaemia induced by increased basal rates.[9,10] The only home studies conducted to date are of short duration and used an investigational device overnight with a laptop-based Kalman filter predictive model controlling insulin delivery by Medtronic Veo system to assess the effect of the system on nocturnal hypoglycaemia.[11,12] In the era of rapidly evolving technology, various models have been used in the development of newer predictive algorithms. The Predictive Low Glucose Management (PLGM) system uses a different predictive algorithm and was evaluated in our centre under standardised in-clinic conditions in real life participants. The system was an investigational device and the predictive algorithm was incorporated in the BlackBerry® Storm smartphone which

controlled the insulin infusion in participants on the Medtronic Paradigm Veo™ insulin pump and Enlite™ glucose sensor with MiniLink™ REAL-Time transmitter. The system was tested with moderate-intensity exercise, excess subcutaneous insulin bolus and increased overnight basal rates which are common triggers of hypoglycaemia. With each hypoglycaemic stimulus, participants were randomised to a control arm with SAPT alone and an intervention arm with PLGM. The system suspended basal insulin when the sensor glucose was predicted to be 4.4mmol/l and found a reduction in the need for treatment of hypoglycaemia in all three settings in the intervention arm.[13] PLGM was also tested under in-clinic conditions in the PILGRIM study. There was reduction in hypoglycaemia with manual insulin bolus when administered to virtual patients and with real life patients when exercised.[14]

Guided by the results of the in-clinic studies, the home trial was designed to evaluate the efficacy of the PLGM system in free-living conditions. The PLGM system is available in the Medtronic MiniMed® 640G pump (Medtronic MiniMed, Northridge, CA) as the 'Suspend before low' feature which automatically suspends basal insulin infusion when hypoglycaemia is predicted. This system is evaluated in the home trial. In contrast to the PLGM in-clinic study, the home trial is of a longer duration, evaluates spontaneous rather than induced hypoglycaemia, and uses sensor glucose values rather than plasma glucose values to quantify hypoglycaemia. Although this system is commercially available, there are as yet no randomised controlled home trials evaluating its efficacy in real life situations. A recent study with the system used for four weeks has shown that it can avoid hypoglycaemia and is acceptable to patients.[15] Our study is the first randomised controlled home trial testing the suspend before low function using the Medtronic MiniMed®640G pump in free living conditions. Apart from the glycaemic data, the six month duration of the study provides the ability to assess the impact of the system in both children and their caregivers.

We hypothesise that the PLGM system will reduce the time spent hypoglycaemic with time spent in hypoglycaemia reduced by at least 40% during six months of therapy with SAPT and Suspend before low vs. SAPT alone in patients with Type 1 diabetes. The system will also not result in an increase in hyperglycaemia or ketosis and will not result in a deterioration of glycaemic control as compared to standard SAPT. We further hypothesize that PLGM will improve hypoglycaemia awareness by reducing hypoglycaemia and will have a positive impact on the quality of life and reduce the fear of hypoglycaemia as

determined by participant/parent questionnaires. Finally, the patient acceptability of the PLGM system will be no worse than their acceptability of standard SAPT.

## AIMS

The primary objective of the study is to compare the average percentage of time spent hypoglycaemic (sensor glucose level <3.5mmol/l) during six months of therapy with SAPT and Suspend before low vs. SAPT alone. The secondary objectives are to compare events of hypoglycaemia, defined as 20 minutes or more with sensor glucose < 3.5mmol/l, during six months of therapy in both groups and to compare the average percentage of time spent hypoglycaemic (sensor glucose level <3.0mmol/l), in target range (sensor glucose 3.5 to 10mmol/l) and hyperglycaemic (sensor glucose level 10-15mmol/l and >15mmol/l). The study will also evaluate the time spent hypoglycaemic during day and night times. In addition, we aim to determine the safety of the system by determining the number of ketosis events (blood ketones >0.6mmol/l) and assess glycaemic control as measured by HbA1c at the end of six months. The study will also determine the counter-regulatory hormone responses to hypoglycaemia, evaluated during a hyperinsulinaemic hypoglycaemic clamp study, in a subgroup of participants with IAH. Hypoglycaemia awareness and the impact of diabetes on patient's quality of life, fear of hypoglycaemia, patient satisfaction and acceptability of the system will be evaluated using validated questionnaires administered at baseline, three months and end of the study.

The outcome or endpoint measures are based on the sensor glucose levels as predefined above. The other measures include the counter-regulatory hormone responses and adrenergic symptoms during hyperinsulinaemic hypoglycaemic clamp study, number of ketosis events defined as blood ketone >0.6mmol/L, the incidence of moderate and severe hypoglycaemia, HbA1c and the questionnaire scores at baseline, 3 months and 6 months of the study. Here, we provide methodological details of the PLGM home trial.

## METHODS

This is a multicentre, unblinded, parallel, randomised controlled phase 3 home trial designed and conducted by five tertiary paediatric diabetes centres in Australia. The trial has been approved by Princess Margaret Hospital, Perth (HREC/2013121EP); The Children's Hospital

at Westmead, Sydney (HREC/13/SCHN/405); John Hunter Children's Hospital, Newcastle (HREC/13/HNE/506); Royal Children's Hospital, Melbourne (HREC/13/HME/506); and Women's and Children's Hospital, Adelaide (HREC/13/WCHN/172). The trial is prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12614000510640). Inclusion and exclusion criteria are summarised in Table 1.

As this is a new system evaluating safety, we included older children and adolescents with type 1 diabetes on continuous insulin pump therapy (CSII). We recruit patients with HbA1c <10% to reflect a clinic cohort and to exclude participants who are less likely to comply and adhere to the protocol. Participants are approached through the diabetes clinics and are screened for eligibility in the study. Written informed consent is obtained from participants aged ≥18 years and written parental consent and participant assent for those < 18 years. Consent is attained by the research nurse or the doctor, who is not directly involved in the routine care of the patient and their families. A participant may decide to withdraw from the study at any time without prejudice to their future care. The study duration for each participant is six months from randomisation. Based on previous unpublished data in a similar cohort of children and adolescents conducted in our centre, the control group is expected to spend on average 5.79% of the time with glucose level <3.5mmol/L, with a standard deviation of 4.87%. 71 subjects would be required in each group to have 80% power to detect a decrease of 2.3% (40% reduction or effect size of 0.475) in time spent with glucose level <3.5mmol/L. It is anticipated that 175 participants would be recruited based on the estimated dropout rate of 20% to ensure a total of 142 participants for the duration of the trial with at least 71 participants in each arm. Recruitment will cease once this target is achieved. The study commenced in August 2014 and is currently ongoing.

**PLGM system**

The predictive algorithm is available in the commercially available Medtronic MiniMed® 640G pump (Medtronic MiniMed, Northridge, CA) designed for continuous subcutaneous insulin infusion (CSII) integrated with real-time continuous glucose monitoring (CGM). The system consists of the Medtronic MiniMed® 640G pump, CONTOUR NEXT LINK wireless blood glucose meter, Enlite™ glucose sensor and Guardian™ 2 Link transmitter. The transmitter sends the sensor glucose data wirelessly every five minutes to the pump and thereby provides real-time glucose measurements and trends. Calibration is required at least

once every 12 hours. The pump is uploaded to transfer information to Medtronic CareLink® therapy Management Software through the use of CONTOUR NEXT LINK glucose meter which is also the uploading device.

'Suspend before low' is a SmartGuard function in the pump and suspends basal insulin infusion when sensor glucose is predicted to be below the set low limit in 30 minutes. The pump suspends basal insulin infusion when two criteria are met; the sensor glucose is at or within 3.9mmol/l (70mg/dl) above the set low limit and is predicted to be 1.1mmol/l (20mg/dl) above the set low limit in 30 minutes. The low limit is set for the entire study at 3.4mmol/l and the pump would therefore suspend insulin infusion when the sensor glucose is ≤7.3mmol/l (3.9+3.4) and predicted to be 4.5mmol/l (3.4+1.1) in 30 minutes. If the alert before low is on, the patient will receive an alert when insulin delivery is suspended. Once the pump is suspended, the insulin infusion will resume after a maximum suspend period of two hours or according to auto-resumption parameters if there is no patient interaction. Basal insulin will automatically resume if sensor glucose is above the low limit and trending upward and insulin has been suspended for at least 30 minutes. However, the infusion may be resumed earlier if the patient intervenes during the suspend time and overrides the suspend function. The auto-resumption feature was not present in LGS wherein the pump had a full two hour pump suspension in the absence of patient intervention and is novel to the predictive algorithm to reduce the potential of post suspend hyperglycaemia.

In the study, the low limit is set for Suspend before low feature. As previous in-clinic studies were evaluated with a suspend threshold of 80mg/dL or 4.4mmol/L[13], we maintained a similar threshold for the home study. As one of the purposes of this trial is to ensure safety of the system at an acceptable threshold which can also prevent hypoglycaemia, the low limit is set for the whole study to maintain uniformity in the intervention group and to enable comparison. However, in real life, this low limit can be altered and the patient can have different low limits for the time of the day.

**Study Protocol:**

**VISITS 1 and 2: Training**

As shown in Figure 1, the first two visits are for training the participants; visit 1 for pump start and training and visit 2 for sensor training. Visits 1 and 2 are combined for participants

previously competent with sensor use while in sensor naïve participants; visit 2 is undertaken at least four days after visit 1. During these visits, participants are also trained to upload the pump from home and are familiarised with sensor alerts and alarms. Sensor alerts and alarms are individualised for participants though every participant has the alert on low turned on at 3.4mmol/l. Questionnaires are administered to participants and/or their parents at this visit. These include Clarke's hypoglycaemia awareness questionnaire,[16] EQ-5D-Y and paediatric specific diabetes quality of life (PedsQL) questionnaires,[17] Hypoglycaemia Fear Survey,[18] and the Pump Satisfaction questionnaire.

**Run-in-period**

The two week run-in period is designed to establish competent use of the system and thereby identify subjects who are not likely to comply with the protocol. All participants are required to use CGM for >80% of the time during the run-in period and are to upload their pump for review by the investigators. Sensor naïve participants are provided an additional week of CGM use to warrant adequate training and familiarisation. The sensor data is reviewed prior to randomisation to ensure a cohort that has and is prone to hypoglycaemia. The participant should have one or more sensor values <3.5mmol/l at any time during the period of CGM use or one or more sensor values <4.4mmol/l on at least three different days. If the CGM is used successfully and the prerequisite criteria are met during the run-in period, participants return for visit 3.

**VISIT 3: Randomisation**

At this visit, measurement of HbA1c, height and weight are obtained and incidence of moderate and severe hypoglycaemia is recorded from the patient and medical records. Moderate hypoglycaemia is defined as any episode of hypoglycaemia during which the child/adolescent was lethargic, disoriented, confused and required third party assistance while severe hypoglycaemia is defined as an episode of loss of consciousness or seizure.[19] Minimisation of variation in gender, age, HbA1c and hypoglycaemia unawareness score is undertaken at randomisation and performed using appropriate software (MinimPy).[20] Minimisation is a method of ensuring excellent balance between groups for known prognostic factors.[21] Randomisations are undertaken by the delegated persons at Princess Margaret Hospital .Participants are randomised to standard therapy with SAPT alone (control group) or SAPT and Suspend before low (intervention group). Suspend on low function is turned off in the control group. Participants in both groups are instructed on ketone testing; before

breakfast and pre-bed in both groups and also at pump resumption after two hours of suspend in the intervention group during awake hours. They are also advised to test for ketones with glucose >15mmol/l or when unwell as part of routine diabetes care. [22] They are instructed to contact the on-call paediatric endocrinologist or paediatrician for advice if required. Ketone data are uploaded at the study visits 4 and 5. Participants are encouraged to upload their pump fortnightly and are provided with a home record log book to document hypoglycaemia, ketosis and sensor or pump related events. Participants are advised to confirm all sensor alerts (on high, low and suspend) events with a capillary blood glucose. The diabetes educator/study nurse will be in contact with participants regularly to provide any support needed and to ensure recording of adverse events

**VISITS 4 and 5: Follow-up visits**

At the follow-up visits at three months (Visit 4) and six months (Visit 5), the diabetes educator/study nurse ensures that all information has been uploaded from the pump and ketone meter. A measurement of HbA1c, height and weight will be obtained along with record of moderate and severe hypoglycaemic episodes during this period. Participants and/or their parents' complete a quality of life questionnaire (EQ-5D-Y, PedsQL), Hypoglycaemia Fear Survey, Clarke's hypoglycaemia awareness questionnaire and the Pump Satisfaction Questionnaire during these visits.

**Hyperinsulinaemic Hypoglycaemic Clamps for participants with impaired hypoglycaemia awareness**

A score ≥4 on Clarke's questionnaire indicates IAH[15] and participants with IAH and above 12 years of age are eligible for hyperinsulinaemic hypoglycaemic clamp studies which will determine the counter-regulatory responses to hypoglycaemia. The studies will be performed at baseline and after six months, irrespective of whether the participant is in the control or intervention group. The clamp procedure will involve infusing insulin intravenously at a constant rate of 80mU/m$^2$ per minute and plasma glucose targets will be achieved by adjusting the rate of infusion of a solution of 20% glucose in water. Prior to induction of hypoglycaemia, plasma glucose will be maintained in euglycaemia (5-6mmol/l) for 60 minutes followed by gradual reduction over 30 minutes to a nadir of 2.8mmol/l. This controlled decline will be guided by plasma blood glucose measurements taken at 5-minute intervals. The blood glucose concentration of 2.8mmol/l will be maintained for 40 minutes before euglycaemia will be restored. For the duration of the clamp procedure, blood glucose

will be measured using glucose oxidase technique with a bedside YSI analyser. Venous blood will be sampled during the euglycaemic and hypoglycaemic phase to determine plasma insulin, glucagon, epinephrine, norepinephrine, cortisol, and growth hormone concentrations during both study days.

## DATA MANAGEMENT AND MONITORING

At consent, each subject will be given a unique identifying number based on their centre. The de-identified information with the patient's unique identifier code will be sent to the data manager in Perth will be used for data input to the centralized database. Data will be stored in a secure office and on password-protected computer files at Princess Margaret Hospital.
A data safety and monitoring board (DSMB) scrutinises conduct of the study team and reviews data arising from the study.

All adverse events defined as a clinical sign, symptom or condition that is causally related to the device implantation procedure, the presence of the device, or the performance of the device system will be recorded and evaluated by the local investigator. Serious adverse event is defined as one which is fatal or life threatening or requires hospitalization for diabetic ketoacidosis or severe hypoglycaemia. Adverse events and serious adverse events will be reported to the DSMB and the ethics at each centre for their review.

## STATISTICAL ANALYSIS

The analysis population will be the intention-to-treat population, which is defined as all patients who are randomised and have at least one visit after baseline. P-values <0.05 will be considered statistically significant and 2-sided P-values will be reported. The time spent hypoglycaemic or hyperglycaemic and the continuous outcome measures will be analysed using a likelihood-based, mixed-effects model repeated measures (MMRM) approach. Rates of hypoglycaemia as well as incidence of moderate and severe hypoglycaemia will be analysed as unadjusted incidence rates based on the Poisson distribution. Incidence rates and incidence rate differences will be presented with their associated 95% confidence intervals calculated as exact Poisson confidence limits. Number of ketosis events and other safety outcomes will be tabulated and presented as n and %. The counter-regulatory hormone

response responses to hypoglycaemia measured during the hyperinsulinaemic hypoglycaemic clamp study in participants with IAH will be presented with descriptive statistics.

## DISCUSSION

This is the first multicentre randomised controlled home trial evaluating the performance of the 'Suspend before low' function in free-living conditions. Apart from the glycaemic data, the safety of the system can be monitored with ketones in both treatment groups. In addition, the six month study duration will provide us the ability to evaluate the psychological outcomes specifically addressing quality of life and fear of hypoglycaemia in both patients and their care-givers. The clamp data will also inform us the counter-regulatory hormone responses in participants with IAH. An improvement in hormonal responses, if demonstrated, will enable us to use this this system as a tool in this high risk group to help restore awareness of hypoglycaemia.

SAPT with Suspend before low feature represents an important advancement in insulin delivery systems because of its potential in reduction of hypoglycaemia. This study will be the first to quantify these effects in a randomised controlled trial in patients with Type 1 diabetes who are predisposed to hypoglycaemia, and the results will provide a benchmark for further studies of automated insulin delivery systems.

**Contributors:** TJ, ED, GA, FC, BK and JF conceived the study design, and TL, NP, HR, MA and JN contributed to the conception of the design. MA drafted the manuscript, and all authors reviewed the draft of the manuscript. All authors approved the final manuscript to be published.

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analysis and interpretation of the data; the preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

**Competing Interests:** This is an investigator initiated trial. All authors declare that there are no competing interests.

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**Table 1:** Inclusion and Exclusion Criteria for PLGM home trial

| **Inclusion criteria** | **Exclusion criteria** |
|---|---|
| Age: 8 to 20 years | Medical conditions predisposing to hypoglycaemia other than diabetes |
| Duration of Type 1 diabetes ≥1 year | Oral glycaemic medications e.g. metformin, sulphonylureas |
| On CSII ≥ 6 months | Inability or refusal to meet protocol requirements |
| HbA1c at eligibility <10% (86mmol/mol) | Pregnancy |

**Figure 1**: Study visits

Flow diagram represents the visits of the study.

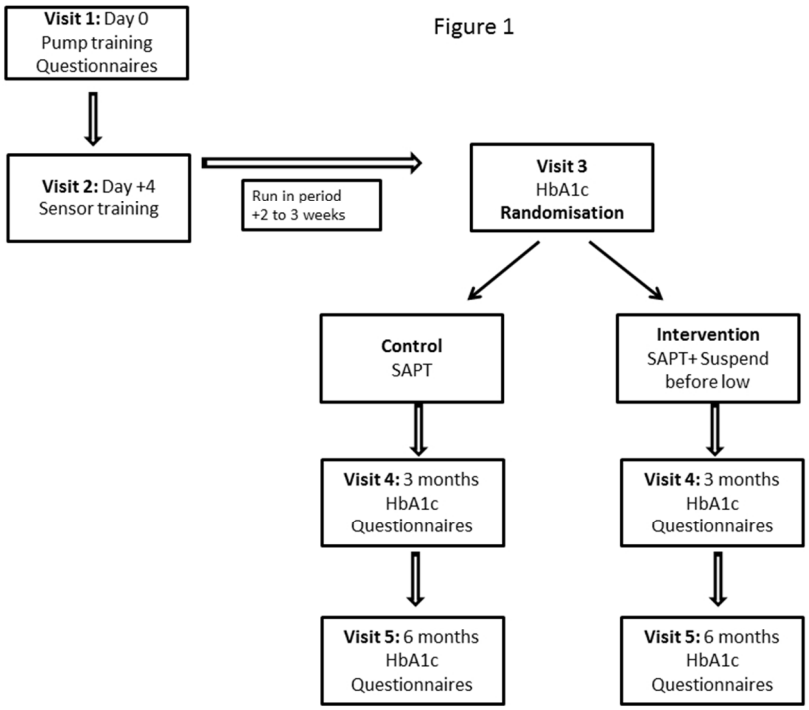


Figure 1

Study visits.
Flow diagram represents the visits of the study.
81x60mm (300 x 300 DPI)


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

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | _____1_____ |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | _____7_____ |
| | 2b | All items from the World Health Organization Trial Registration Data Set | _____ |
| Protocol version | 3 | Date and version identifier | ___version3___ |
| Funding | 4 | Sources and types of financial, material, and other support | ____12_____ |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | ____12_____ |
| | 5b | Name and contact information for the trial sponsor | ____12_____ |
| | 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 | ____12_____ |
| | 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) | ____11_____ |

| | | | |
|---|---|---|---|
| **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 | 4,5 |
| | 6b | Explanation for choice of comparators | 9 |
| 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, noninferiority, exploratory) | 6 |
| **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 | 6,7 |
| 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) | 7,15 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 8,9,10 |
| | 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) | 7 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 9 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 15 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 6 |
| 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) | figure 1 |

| | | | |
|---|---|---|---|
| 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 | 7,9 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 9 |
| 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 | 9 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 9 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 6 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | NA |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 11,14 |
| | 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 | - |

| | | | |
|---|---|---|---|
| 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 | 11,12 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 11 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 11 |
| | 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) | 11 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 11 |
| | 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 | - |
| 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 | 11 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | - |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 6,7 |
| 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) | - |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 7 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | - |
| 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 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 13 |
| 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 | - |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | - |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | nil |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | |
| 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 | |

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