UNIVERSITY OF BIRMINGHAM

PROTOCOL
ERN_2934

PROTOCOL

Title page

Full/long title of the project

The effect of interrupting sitting with regular active breaks on peripheral and cerebral blood flow in adults with type 1 diabetes

Short title/acronym

Sitting and vascular health in people with T1D

Protocol version number and date

Protocol version number:	1.0
Protocol version date:	09/09/2024

Research reference numbers

IRAS number:	338230
Sponsor/RG number:	RG_24-066
REC reference number:	2934
Public registry number:	
Funder number:	

Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the CI agrees to adhere to the signed University of Birmingham's sponsorship CI declaration.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the project will be given; and that any discrepancies from the project as planned in this protocol will be explained.

Full project title:	The effect of interrupting sitting with regular active breaks on peripheral and cerebral blood flow in adults with type 1 diabetes
Protocol version number:	2.0
Protocol version date:	10/02/2025

Chief Investigator (CI)	
Name:	Dr Katie Hesketh
Date:	10/02/2025
Signature:	

Sponsor statement

Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

Table of contents

Key contacts

Role/function	Contact details
Principal Investigator	Dr Katie Hesketh, k.l.hesketh@bham.ac.uk
PhD researcher	Joseph Jenkins, jgj301@student.bham.ac.uk

Project summary

Study Title	The effect of interrupting sitting with regular active breaks on peripheral and cerebral blood flow in adults with type 1 diabetes	
Internal ref. no. / short title	Sitting and vascular health in people with T1D (ERN no: 2934)	
Proposed start date	01/02/2025	
Proposed end date	01/08/2026	
Countries in which the study will take place	England	
Study Design	Randomised crossover trial	
Study Participants	Habitually sedentary people type 1 diabetes using a closed-loop insulin delivery system	
Planned Sample Size	24	
Planned Study Period	18 months	
	Objectives	**Outcome Measures**
Primary	To determine the effect of active breaks on change in superficial femoral artery flow-mediated dilation (FMD) compared to 7 hours compared to uninterrupted sitting.	Femoral artery FMD
Secondary	To determine the effect active breaks compared to 7 hours of uninterrupted sitting on markers of glycaemia as assessed by continuous glucose monitoring (CGM). Glucose data gathered from closed-loop systems will be split into three time blocks; 1). 48 hours prior to the experimental period; 2). Experimental period (~7 hours); 3). 48 hours post-experimental period.	a) mean glucose b) % of time in level 2 hypoglycaemia (<3.0mmol/L) c) % of time in level 1 hypoglycaemia (3.0-3.9mmol/L) d) % of time in level 1 hyperglycaemia (10.0-13.9mmol/L) e) % of time in level 2 hyperglycaemia (>13.9mmol/L) f) glycaemic variability, reported as CV and SD g) episodes of hypoglycaemia and hyperglycaemia h) area under the curve of episodes of hypoglycaemia and hyperglycaemia.
	To determine the effect of active breaks on insulin dose compared to 7 hours compared to uninterrupted sitting.	Closed-loop insulin delivery system

	To determine the effect of active breaks on cerebrovascular function compared to 7 hours of uninterrupted sitting.	Middle cerebral artery velocity (MCAv)
	To determine the effect of active breaks on markers of inflammation	1) Endothelin-1 (ET-1) concentrations 2) Vascular cellular adhesion molecule concentrations (VCAM-1) 3) Intracellular adhesion molecule (ICAM-1) 4) Interleukin 6 (IL-6) concentrations

Funding and support in kind

Funder(s)	Financial and non-financial support given
Na	Na

Role of sponsor and funder

Roles & responsibilities of management committees/groups & individuals

Patient & public involvement group

Exercise for Type One Diabetes (EXTOD) PPI group

Protocol contributors

Dr Katie Hesketh (University of Birmingham)
Mr Joseph Jenkins (University of Birmingham)
Dr Sam Lucas (University of Birmingham)
Dr Catarina Rendeiro (University of Birmingham)
Dr Parth Narendran (University of Birmingham, Queen Elizabeth Hospital Birmingham)
Dr Matthew Cocks (Liverpool John Moores University)
Dr Joseph Maxwell (Liverpool John Moores University)
Dr Tiago Pecanha (Manchester Metropolitan University)

Key words

activity breaks; glycemia; closed-loop; prolonged sitting; flow-mediated dilation

Project flow chart

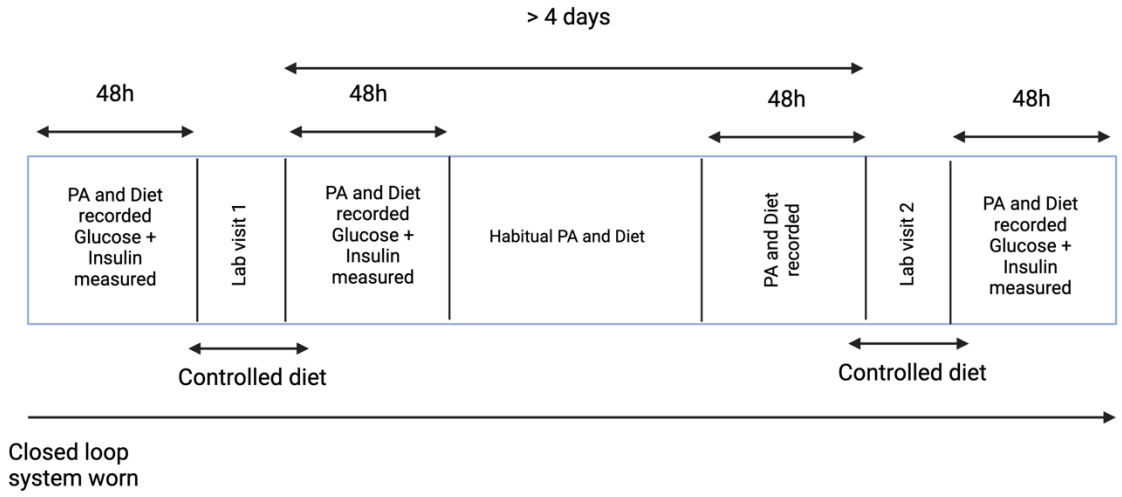

Figure 1. Study timeline schematic. PA, physical activity.

Protocol

1. Background

The primary cause of mortality in people with T1D is cardiovascular disease (CVD) (Secrest et al., 2010). As such, individuals with T1D have a 3 times greater risk of developing CVD over their lifetime compared to the general population, with CVD events tending to occur earlier (Liese et al., 2013; Rawshani et al., 2017; Secrest et al., 2010). Diabetic vasculopathy often precedes overt symptoms of CVD such as atherosclerosis and is thought to be primarily driven by vascular dysfunction (Longendyke et al., 2023).

Sedentary behaviour has been identified as a risk factor for morbidity and mortality, independent of whether the general physical activity guidelines are being met (Biswas et al., 2015; Chau et al., 2013). Recent studies for individuals with T1D have examined the effect of breaking up prolonged periods of sedentary behaviour; individuals are encouraged to break up their sitting with brief, frequent bouts of standing and/or low-intensity physical activity (Alobaid et al., 2023; Campbell et al., 2023). Previous research on interrupting prolonged sitting has focused on healthy or prediabetic populations (Daniele et al., 2022) or on outcomes related to glucose regulation in T1D populations (Campbell et al., 2023). A recent study by Campbell et al. (2023) first demonstrated the potential of breaking up prolonged sitting to acutely improve glucose regulation in people with T1D. The study design incorporated 3-minute walking breaks (interrupting sitting) every half an hour during a 7-hour experimental window and found a 16% decrease in average glucose concentrations not only during the 7-hour experimental trial but also for 48 hours following the trial (Campbell et al., 2023). To date, the acute effects of breaking up sitting vascular function in T1D populations remain unexplored.

2. Rationale

Therefore, this study will investigate the impact of breaking up 7 hours of sitting with 3-minute intervals of light-intensity walking every 30 minutes on vascular function in individuals with T1D. It is hypothesised that interrupting sitting will acutely improve vascular function and metrics relating to glucose management compared to prolonged sitting.

3. Theoretical framework

To date, the acute effects of breaking up sitting on vascular function in T1D populations remain unexplored. We aim to advance the work of Campbell et al. (2023) by using the same protocol that has shown positive effects on glucose regulation to determine if there are positive effects on other domains of health.

4. Research question/aims

We aim to investigate the influence of interrupting prolonged sitting with scheduled active breaks (3 mins of walking every 30 min) on peripheral and cerebral blood flow in adults with T1D using hybrid closed-loop insulin delivery systems. In addition, we aim to investigate markers of glycaemia, inflammation and total daily insulin dose.

4.1. Objectives

4.2. Outcome

	Objectives	Outcome Measures
Primary	To determine the effect of active breaks on change in superficial femoral artery flow-mediated dilation (FMD) compared to 7 hours compared to uninterrupted sitting.	Femoral artery FMD
Secondary	To determine the effect active breaks compared to 7 hours of uninterrupted sitting on markers of glycaemia as assessed by continuous glucose monitoring (CGM). Glucose data gathered from closed-loop systems will be split into three time blocks; 1). 48 hours prior to the experimental period; 2). Experimental period (~7 hours); 3). 48 hours post-experimental period.	i) mean glucose j) % of time in level 2 hypoglycaemia (<3.0mmol/L) k) % of time in level 1 hypoglycaemia (3.0-3.9mmol/L) l) % of time in level 1 hyperglycaemia (10.0-13.9mmol/L) m) % of time in level 2 hyperglycaemia (>13.9mmol/L) n) glycaemic variability, reported as CV and SD o) episodes of hypoglycaemia and hyperglycaemia p) area under the curve of episodes of hypoglycaemia and hyperglycaemia.
	To determine the effect of active breaks on insulin dose compared to 7 hours compared to uninterrupted sitting.	Closed-loop insulin delivery system
	To determine the effect of active breaks on cerebrovascular function compared to 7 hours of uninterrupted sitting.	Middle cerebral artery velocity (MCAv)
	To determine the effect of active breaks on markers of inflammation compared to 7 hours of uninterrupted sitting	5) Endothelin-1 (ET-1) concentrations 6) Vascular cellular adhesion molecule concentrations (VCAM-1) 7) Intracellular adhesion molecule (ICAM-1)

5. Design and methods of data collection and data analysis

Study design: The study will use a randomised, crossover design, in which the same participants will complete two 7-hour experimental trials. One condition will involve participants sitting uninterrupted for 7-hours (*Sedentary*), while the other condition will require participants to interrupt 7-hours of sitting with 3-minutes of light-intensity walking every 30 minutes (*Active Breaks*). During both conditions, blood flow (peripheral and cerebral), arterial diameter and blood markers will be measured on two separate occasions (baseline and post (7hrs)). Interstitial glucose levels and insulin administrated by the hybrid closed loop will be recorded 7 days prior to, during and 7 days following each trial visit. Diet and physical activity for each participant will be controlled for 24-hours prior to and during and for the evening following each visit each trial visit.

The study will use a randomised, counterbalanced, crossover design, whereby participants will complete two experimental periods, each period will include a laboratory visit where the effects of 7 hours exposure to one of either 2 conditions will be investigated:

A. Continuous sitting *(Sedentary)*
B. 3 minutes of light-intensity walking every 30 minutes *(Active Breaks)*

Lab visits will be identical except for the condition and will be separated by at least 4 days. Females will be tested in the early follicular phase of the menstrual cycle to control for hormonal fluctuations. Female participants will be provided with the option to opt-out of a question relating to the menstrual cycle during the questionnaire and are welcome to talk to a female member of the research team on request. If they do not wish to disclose this information, then they will be excluded from the study and will not complete any further procedures.

Pre-experimental procedures

Potential participants will be sent a participant information sheet (PIS) via email. If, after reading the information sheet, they still wish to participate, they will attend a short online video call to discuss the study in more detail. During this video call the participant will have the opportunity to ask any questions about the study and eligibility will be assessed by the research team. Participants will then be asked to electronically sign an informed consent form (Dropbox Sign) in their own time. Should informed consent be gained, participants will complete a study-specific online questionnaire (via MS Forms), asking for data on age, sex, ethnicity, height, weight, medical history (including pregnancy), most recent HbA1c and diabetes history (duration of diabetes, hypoglycaemic events within the past 3 months).

Randomisation and Blinding

The order of condition will be randomised to either the *Sedentary* or *Active Breaks* conditions using a computer-generated random allocation sequence. Due to the nature of the study, blinding of the participants or researchers is not possible, however, participants and researchers will be blinded to experimental condition order (by keeping the order in a sealed envelope) until the morning of the first experimental visit.

Physical activity monitoring, interstitial glucose, insulin and carbohydrate intake

Participants will be provided with an activPAL physical activity monitor to wear for 48 hours prior to the first trial and will be requested to wear a second monitor between trials in order to standardise physical activity. Participants will also be provided with an online diary (MyFitnessPal) to record their diet for 48 hours prior to each trial and for 48 hours following each trial. A member of the research team will set up the MyFitnessPal account. To do this an email address, password, name, date of birth and sex will be entered into the app. The research team will set up a unique user profile for this service. These will be created using no personal details, with study codes used for all personal data entries. Glucose and insulin will be continuously recorded using the closed-loop system. Interstitial glucose will be continuously measured throughout the study period, with participants continuing to use their own continuous glucose monitor for the duration of the study. To access data, the research team will ask participants to share their glucose reports from their device's data management platform (e.g. LibreView for Abbott devices or Dexcom Clarity for Dexcom devices) for 4 weeks prior to the study and for 4 weeks following the study. This will be to ensure behaviour changes that have affected glucose levels have not occurred as a result of enrolling into the study. Once the participant has finished both trials and all research data have been downloaded after 4 weeks, the research team will cease using the glucose and insulin remote data-sharing link.

Standardisation of diet

Participants will be provided with a food diary for 48 hours prior to each lab visit. In addition, two mixed-macronutrient meals (dinner and breakfast) will be provided for participants to consume at home on the evening prior to (between 17:00-20:00) and on the morning of each lab visit (between 06:00-07:00). These meals will be home delivered, using a food delivery service on the days leading up to each lab visit. A third mixed-macronutrient meal will be provided for participants to consume on the day of each lab visit. All food will be pre-packaged and commercially available, with detailed instructions will be given to each participant for when they should consume each item. All meals will aim to provide 33.3% of estimated energy requirements based on body mass, with a target macronutrient profile of 12-15% energy from protein, 30-33% energy from fat, and 53-55% energy from carbohydrate. They will be asked to avoid further food intake other than when it is necessary to prevent or treat a hypoglycaemic event (glucose readings <4mmol.l^{-1}).

Experimental Period

On the morning of each lab visit, participants will be contacted to confirm that they have consumed their standardised meals and that their glucose levels are within the range of 4-10 mmol.l^{-1}. Prior hypoglycaemia has the potential to affect subsequent vascular function measures (Pena et al., 2012). As such, experimental visits will be re-arranged if blood glucose concentrations are not within this range or if participants have experienced one or more sustained (>90 minutes) hyperglycaemic (glucose readings >10mmol.l^{-1}) or sustained (>30 minutes) hypoglycaemic episodes during the previous 24-hours.

Lab Visits

Participants will be asked to avoid cycling or walking to the appointment on the mornings of each trial. They will be encouraged to use motor or public transport, arriving at the laboratory for ~07:30. Upon arriving at the laboratory, participants will be asked to complete a set of validated (Groningen Sleep Scale, International Physical Activity Questionnaire (IPAQ), Hospital Anxiety Depression Scale (IPAQ), SF-12 Health Survey, Diabetes Quality of Life (DQOL)), and non-validated questionnaires (perceived stress) on a computer before laying supine, starting a 60-minute 'steady state' period. This should take approximately 15 minutes. During the following 60 minutes resting blood pressure will be taken using an automatic device, and a superficial femoral artery (SFA) flow mediated dilation (FMD) ultrasound scan will be conducted using the non-invasive procedures described below. A transcranial doppler (TCD) ultrasound will assess cerebral blood velocity (CBv) and a Duplex ultrasound will measure the blood velocity and diameter of the internal carotid artery (ICA). Using a venepuncture, whole blood (3ml) will be sampled from an antecubital vein for the later analysis of baseline endothelin-1 (ET-1) Vascular cellular adhesion molecule (VCAM-1), Intracellular adhesion molecule (ICAM-1) and Interleukin-6 (IL6) concentrations. Blood will be drawn by a trained phlebotomist, and samples stored at -80^{0} until later analysis using the procedures described below. Once this is complete (~09:00), participants will then be supervised while they sit at a workstation in an upright chair, minimising lower body movement.

During this time, food intake will be restricted until lunch (3.5 hrs). However, in the case of a hypoglycaemic episode (blood glucose <4mmol.l^{-1}), participants will be provided with 15g of carbohydrates (Skittles). Blood glucose will be reassessed after 10-minutes. Should blood glucose still be <4.0 mmol/L, further 15 g of carbohydrates will be provided. The process will be repeated until blood glucose returns above 4 mmol.l^{-1}.

During the *Sedentary* trial, participants will remain seated for 7-hours at a workstation where they will have access to the internet and will be able to work, read etc., To replicate free-living conditions, lower body movements will be permitted, however, participants will be encouraged to keep their feet flat on the ground, with their legs uncrossed. During the *Active Breaks* trial, participants will interrupt their 7-hours of sitting every 30 minutes with 3-minute bouts of self-paced, light-intensity walking. The first walking bout will be timed to occur 30 minutes following participants are first seated. Water will be provided *ad libitum* throughout each trial and participants will be encouraged to take bathroom breaks that coincide with their lunch break. During bathroom breaks, a wheelchair will be used to transport participants to the nearest distance to the bathroom from any of the sites (~10m). This will be measured from the seated position to the door of the bathroom.

Following 3.5 hours, lunch will be provided. Participants in the *Active Breaks* group will be instructed to complete their 3-minute walk prior to food consumption. Each participant will be instructed to consume their meal within 20 minutes. On completion of the 7-hour trial, participants will be instructed to lay supine to begin the post-testing measures. After ~60 minutes participants will then leave the lab.

Post-experimental procedures

Participants will be given instructions to continue wearing their activPAL physical activity monitor in order to record physical activity, in addition to recording their diet via MyFitnessPal for 48 hours following the trial. At least 4 days will separate the two trials to avoid wash-over effects.

Participants will receive a £50 Love2Shop voucher after completion of the study (final visit on the final day).

6. Project setting

The study will be conducted across multiple study sites: School of Sport, Exercise and Rehabilitation Sciences (SportExR) at the University of Birmingham (UoB), School of Sport and Exercise Sciences at Liverpool John Moores University (LJMU) and Department of Sport and Exercise Sciences at Manchester Metropolitan University (MMU). All data collection will take place across these sites by a member of the research team.

7. Participant recruitment

7.1. Eligibility criteria

7.1.1. Inclusion criteria

- Having been diagnosed with T1D for more than 3 years
- Aged 18-66 years
- Not currently meeting physical activity guidelines of > 150 min/week of moderate-intensity exercise or >75 min/week of high-intensity exercise
- being sedentary (inactive) form more than 8h per waking day (sitting or lying)
- Spending <5h per day seated or sedentary
- Currently using hybrid closed-loop insulin delivery system

7.1.2. Exclusion criteria

- Under 18 years of age
- Engaging in structured planned exercise (e.g. running, cycling, gym, or sports)
- Pregnant or planning to become pregnant
- <6 months postpartum or stopped breastfeeding <1 month before recruitment
- Having been diagnosed with cerebrovascular or cardiovascular disease
- Having a significant history of uncontrolled hyperglycaemia (HbA1c >85 mmol/mol)
- Having a history of severe hypoglycaemia requiring third party assistance within the last 3 months
- Illness within the last 2 weeks

7.2. Sampling

7.2.1. Size of sample

Twenty-four adults with T1D will be recruited

7.2.2. Sampling technique

Sampling techniques will include a combination of convenience, snowball and purposive sampling. We will use these sampling techniques due to the specific nature of the inclusion criteria of the study and the required sample size.

7.3. Recruitment

Recruitment will take place via several methods. Once a suitable participant has expressed an interest in the study a participant information sheet will be sent to them, and a short initial meeting will be arranged (approx. 30 minutes). Meetings will be via telephone or video link depending on the participants preference. Following assessment of eligibility, the study will be explained detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal. Participants will also be able to ask any questions they may have.

7.3.1. Sample identification

Participants will be sampled through a combination of convenience and snowball sampling, with targeted recruitment based on the relevant inclusion/exclusion criteria of the study via the following methods.

1. Clinical database searches, and subsequent recruitment letters and text messages/SMS from participating diabetes clinics (Queen Elizabeth Hospital, Birmingham) searches will be for patients currently using closed-loop insulin delivery systems
2. Emails sent to volunteers within the ‘research for the future’ consent to approach database
3. Advertisement on the Diabetes UK website through the "take part in research" portal
4. Advertisement on the JDRF UK website through the "opportunities to take part in research" page
5. Advertisement through diabetes support groups
6. Advertisement on social media (e.g. Twitter (X) and Facebook)
7. Advertisements in newspapers
8. Advertisement to businesses through their occupational health team or other appropriate department
9. University of Birmingham and LJMU staff and students: via advertisements around the campus and via internal emails.
10. Posters displayed in high traffic areas within the health care system, diabetes websites and social media

Interested participants will contact the research team via email and be provided with a participant information sheet, unless otherwise stated.

7.3.2. Consent

Following the initial meeting participants will be asked to provide informed consent. If participants wish to take longer to decide this will be possible and no time limit will be placed on this. During this time, participants will be free to question the investigator, their GP or other independent parties to decide whether they wish to participate in the study. The participant will also have a hard copy of the participant information sheet. Patients will sign the Informed Consent document using the eSignature solution(HELLO SIGN), in line with HRA advice (Sept 2018). A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

8. Storage and analysis of human tissue

Blood samples will be stored in freezers located in a card-only access areas within UoB, LJMU and MMU. All samples will be stored in vials labelled by sample and participant ID number that can only be identified by

members of the investigative team. All samples will be stored, accessed, and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities will meet the requirements as set out in the 2004 Human Tissue Act. Samples remaining at the end of the study will be destroyed in accordance with the 2004 Human Tissue Act.

9. Safety reporting

Patients will be asked if an adverse event (AE) (see below for definition) has occurred during meetings held post intervention. Should an AE be reported the study's lead clinician Dr Parth Narendran will assess the event and the end outcome using the Serious Adverse Events Report Form. The PI will then report the event to the sponsor using the SAE Letter Template.

Serious adverse events are defined as any adverse event at any stage in the research participation of the study which:

- results in death
- is life threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly/ birth defect

Life-threatening refers to an event in which the participant was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Expected adverse events include:

- Hypoglycaemia that could deal with by self
- Hyperglycaemia that could deal with by self
- Cough and Colds
- Flu
- Muscle aches and pains
- Muscle strains
- Indigestion
- Constipation
- COVID-19

10. Ethical and regulatory considerations

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki and relevant regulations.

10.1. Assessment and management of risk

Risk of hypoglycaemia: To minimise the risk of hypoglycaemia resulting from an unfamiliar diet, participants will be provided with the macronutrient content of the food so participants can determine the correct dose of insulin. On the day of testing, the participants will be provided with a standardised breakfast, with a calorie content that is matched to their habitual diet. Should participants experience hypoglycaemia during the vascular measurements, they will be treated using a standard protocol. Participants will be provided with 15g of carbohydrates (Skittles). Blood glucose will be reassessed after 10 minutes. Should blood glucose still be <4.0 mmol/l another 15g portion of carbohydrates will be provided. The process will be repeated until blood glucose returns above 4.0 mmol/l. This is a standard procedure within our lab and others. For the rest of the

experimental period participants will be able to control blood sugar as they feel necessary. People with type 1 diabetes are experienced at monitoring their own blood glucose and appropriate actions to take. Finally, the research team also have great experience of running similar projects in people with type 1 diabetes

Ultrasound gel – allergic reaction: Participants will be asked if they have any known allergy to the gel. If so, the participants will not be tested for this measure. However, we do not envisage this to be an issue.

The researcher conducting the tests will monitor the participant for any possible allergic reaction throughout the test, if any signs of an allergic reaction occur then the testing protocol will be stopped and the participant will be referred to their GP.

Prolonged sitting – can lead to deep vein thrombosis (DVT) and pressure sore: Participants will be permitted to move their arms and legs freely and adjust their body position within their chair. This will maintain blood flow and reduce the risk of blood pooling. In addition, participants will be free to get up and move if in pain or discomfort. This will not affect their participation in the study or reimbursement. The participant will be free to stop the testing immediately and withdraw from the study at any time throughout the testing protocol.

Discomfort caused by the occlusion cuff: The participant will be warned before the test commences about the sensation that is caused during this test. The researcher will ensure that the cuff is fitted correctly, and the pressure is set correctly (220 mmHg). The participant will be free to stop the test at any time if they wish. The occlusion cuff will be released and removed; the test will not be continued. The participant will be free to withdraw from the study at any time.

Discomfort caused by the blood sampling needle: The participant will be warned before the test commences about the sensation that is caused during this procedure. The researchers taking the blood samples will be trained in venepuncture.

10.2. Research ethics committee (REC) and other regulatory review & reports

Before the start of the project, a favourable opinion will be sought from NHS REC for the protocol, informed consent forms and other relevant documents.

10.2.1. Regulatory review & compliance

- All correspondence will be retained.
- The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to the HRA for written approval.
- Annual Progress Reports will be submitted to the NHS REC which gave the favourable opinion, the HRA (hra.approval@nhs.net) and the Sponsor on the anniversary of NHS REC Favourable Opinion, and annually thereafter until the End of Study Declaration has been submitted to the NHS REC which gave the favourable opinion, the HRA and the Sponsor.
- Upon the completion of the study an End of Study Declaration (within 90 days of the end of the study) and End of Study Report (within 12 months of the end of the study) will be submitted to the NHS REC which gave the favourable opinion.
- For any amendment to the project, the CI or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The CI or designee will work with sites (R&D departments at NHS sites as well as the project delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the project as amended.
- The University of Birmingham's Clinical Research Compliance Team may carry out compliance visits to monitor adherence with applicable standards and regulations.

10.2.2. Amendments

Approval will be obtained from the University of Birmingham REG for any amendments to, or changes of status in the study prior to submission to the REC that ethically approved the study and any other regulatory authorities. Amendment history will be tracked using Appendix 3 of this document whenever a new version of the protocol is produced.

10.3. Peer review

The final study protocol has been discussed within research groups at UoB, LJMU and MMU.

10.4. Patient & public involvement

Patient facing documents have been reviewed by the EXTOD-Active PPI group.

10.5. Protocol compliance

Accidental protocol deviations can happen at any time. They will be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach. Serious breaches will be communicated to the sponsor by email.

The quality of the study will be assured through the series of management groups. The Local Delivery Group (PI, KH and JJ) will hold weekly meetings to discuss progress. These discussions will feed directly into monthly Trial Delivery Meeting between all co-investigators.

10.6. Data protection and confidentiality

Participant confidentiality will be maintained at all times and the project will be compliant with the requirements of the Data Protection Act 2018. All investigators and site staff will comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

All files will be pseudonymised at the time of collection. All data will be kept on password protected University computers and laptops or in locked filling cabinets. An electronic and paper copy of the pseudonymisation key will be kept, these will be stored electronically on a networked PC in a password protected document or in a locked filing cabinet. Following completion of the study the pseudonymised data will be stored on a network attached data storage system. Only the principal investigator and members of the research team will have password-protected access to this storage unit. Access to the data is dependent on correct input of personal login details. The PI (KH) will be the designated data custodian.

10.7. Indemnity

University of Birmingham has Clinical Trials insurance to cover the legal liability of the University as Research Sponsor in the eventuality of harm to a research participant arising from management and design of the research by the University and the activities here are included within that coverage.

University of Birmingham Clinical Trials insurance policies provide an indemnity to our employees and students for their potential liability for harm to participants during the conduct of the research and the activities here are included within that coverage.

10.8. End of study and archiving

The end of study is the last test of the last subject. Any personal data collected which is not fundamental to the research will be destroyed; however, consent forms need to be kept for 10 years in line with the University of Birmingham policy. Study data will be stored on password-protected computers at the University of Birmingham. Only designated members of the research team may have access to this documentation, to check the results or that the study has been conducted properly.

10.9. Access to the final dataset

Only the research group at University of Birmingham will have access to the full study dataset. If a formal request is received and approved by the trial delivery group, the study will allow site investigators to access the full dataset.

11. Dissemination policy

11.1. Dissemination policy

Upon study completion, the chief investigator owns data. On completion of the study, the data will be analysed, and results will be disseminated via publication in clinical and physiological journals, presented at National and International conferences and in the form of feedback sheets or perhaps local articles. All participants will also be offered a debriefing meeting whereby the researcher will discuss research findings with them. Participants will not be identifiable from the results of the study.

11.2. Authorship eligibility guidelines and any intended use of professional writers

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

12. References

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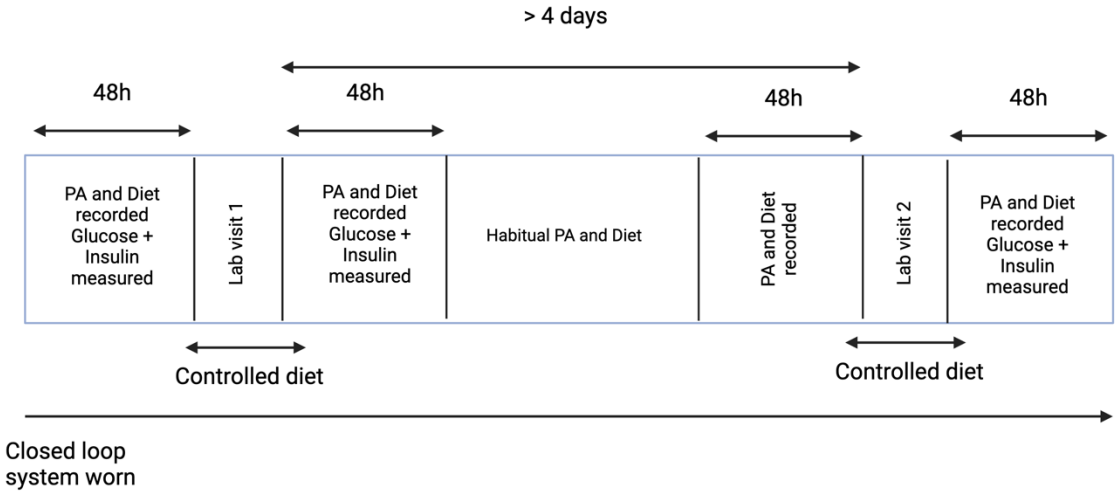
13. Appendices

13.1. Appendix 1 – required documentation

13.2. Appendix 2 – schedule of procedures



13.3. Appendix 3 – amendment history

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version				
Amendment number	**Date of amendment**	**Protocol version number**	**Type of amendment**	**Summary of amendment**