Full Study Title

**RESPONSE** - Breaking up prolonged sitting in people with type 2 diabetes: Optimising the response

Confidentiality Statement

All information contained within this protocol is regarded as and must be kept confidential.  No part of it may be disclosed by any Receiving Party to any Third Party, at any time, or in any form without the express written permission from the Chief Author/Investigator and / or Sponsor.

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| **Sponsor:** | University of Leicester |
| **Sponsor Reference No:** | 0791 |
| **Ethics Ref (IRAS Project ID):** | 281671 |
| **Funder:** | Leicester NIHR Biomedical Research Centre and NIHR Senior Investigator Funds and Leicester Diabetes Centre |
| **Date and Version No:** | 20.08.2020  Version 1.0 |
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# AMENDMENT HISTORY

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| --- | --- | --- | --- | --- |
| **Amendment No.** | **Protocol Version No.** | **Date issued** | **Author(s) of changes** | **Details of Changes made** |
|  |  |  |  |  |

# SYNOPSIS

|  |  |
| --- | --- |
| **Study Title** | RESPONSE- Breaking up prolonged sitting in people with type 2 diabetes: Optimising the response |
| **Internal ref. no.** | N/A |
|  |  |
| **Trial Design** | Randomised intervention with pre and post measurement conditions at both time points. |
| **Trial Participants** | People with a diagnosis of T2DM on mono- or dual-therapy with HbA1c between 6.5 and 9 % |
| **Planned Sample Size** | 25 |
| **Follow-up duration** | N/A |
| **Planned Trial Period** | November 2020 – June 2022 |
| **Primary Objective** | Part 1 – Lab-based  To quantify affective responses to different activities used to break up prolonged sitting time.  Part 2 – Intervention  To investigate whether personalised recommendations for reductions in prolonged sitting time with respect to time and type are more effective than generic advice for improving glucose control over a 4-week intervention. |
| **Secondary Objectives** | Part 1 – Lab-based   * To quantify the rate of perceived exertion of different activities used for breaking up prolonged sitting time * To quantify the energy expenditure of different activities used for breaking up prolonged sitting time * To quantify degree of muscle activation of different activities used for breaking up prolonged sitting time * To investigate whether affective responses, perceived exertion, energy expenditure, muscle activation, and the degree of pain observed across different activities used to break up prolonged sitting time are associated with key descriptive characteristics   Part 2 – Intervention   * To investigate whether fasting metabolic markers (glucose, insulin, lipid profile) are changed following the intervention. * To investigate whether variability in blood glucose (weekly average) and time spent in hypo- and hyper-glycaemia change at the end of the intervention as assessed via Continuous Glucose Monitor. * To investigate whether physical function is improved following the intervention. * To investigate changes to overall sedentary behaviour, sleep, and physical activity during and at the end of the intervention. |

# ABBREVIATIONS

**AE** Adverse Event

**AR** Adverse Reaction

**AUC** Area Under the Curve

**CFQ-11** Chalder Fatigue Scale

**CGMS** Continuous Glucose Monitoring System

**CI** Confidence Interval

**COVID-19** (see SARS-CoV-2)

**CRF** Case Report Form

**CRN** Clinical Research Network

**CT** Clinical Trials

**EC** Ethics Committee (see REC)

**eFI** Electronic Frailty Index

**EMG** Electromyography

**EQ-5D-5L** EuroQual-5 Dimension-5 Level

**GCP** Good Clinical Practice

**GP** General Practitioner

**GST-CON** Generic Sitting Time Control

**HADS** Hospital Anxiety and Depression Scale

**HbA1c** Haemoglobin A1c

**HGS** Handgrip Strength

**HR** Heart Rate

**ICF** Informed Consent Form

**IRAS** Integrated Research Application System

**ISWT** Incremental Shuttle Walk Test

**Kcal** Kilocalories

**METs** Metabolic Equivalents

**mMRC** Modified Medical Research Council

**mPPT** Modified Physical Performance Test

**PA** Physical Activity

**PI** Principal Investigator

**PIL** Participant Information Letter

**PIS** Participant Information Sheet

**PST-INT** Personalised Sitting Time Intervention

**R&D** NHS Trust R&D Department

**REC** Research Ethics Committee

**RER** Respiratory Exchange Ratio

**RMR** Resting Metabolic Rate

**RPE** Rate of Perceived Exertion

**SAE** Serious Adverse Event

**SAR** Serious Adverse Reaction

**Sarc-F** Strength-Assistance in walking-Rise from chair-Climb stairs-Falls

**SARS-CoV-2** Severe Acute Respiratory Syndrome Coronavirus 2

**SD** Standard Deviation

**SPPB** Short Physical Performance Battery

**SUSAR** Suspected Unexpected Serious Adverse Reactions

**T2DM** Type 2 Diabetes Mellitus

**TMF** Trial Master File

**UK** United Kingdom

**UKDDQ** United Kingdom Diet and Diabetes Questionnaire

**VO2**Volume of Oxygen

**WHO** World Health Organisation

**WHO-DAS** World Health Organisation Disability Assessment Schedule

**W.min** Watts per Minute

# BACKGROUND AND RATIONALE

Type 2 Diabetes Mellitus

T2DM is a condition characterised by hyperglycaemia, resulting from defects in hepatic and peripheral glucose uptake, insulin secretion, or a combination of these.1 The current estimates from the International Diabetes Federation suggest there to be around 463 million adults living with some form of diabetes throughout the world, with the most common form being T2DM.2 Current predictions suggest that, unless changes are made, by 2030 the number of cases will increase to around 578 million, and 625 million by 2045.3 Persons suffering from T2DM are considerably more likely to have impaired physical function compared to their healthy counterparts.4 Further to this, the physiological changes which occur in T2DM make patients extremely high risk for the development of CVD, which is the leading cause of death in persons with T2DM.5 Therefore, in order to inform future lifestyle management, it is necessary to explore the role of potentially modifiable determinants such as physical activity, sedentary behaviour, and prolonged sitting time.

Physical Activity, sedentary behaviour, and sitting time

Some of the most beneficial lifestyle factors which, when optimised, can enhance health and improve postprandial hyperglycaemia are physical activity, sedentary behaviour, and prolonged sitting time. Physical activity is any bodily movement in which energy expenditure is raised above that at rest.6A behaviour is considered sedentary when it remains ≤1.5 METs; anything above this falls within the realm of physical activity.7,8 Sitting time is defined as any prolonged time during which one’s weight is supported by the buttocks, with the back upright. This can be further classified into active and passive sitting, depending on energy expenditure: >1.5 METs (Active) or ≤1.5 METs (Passive).8

Consequences of too much sitting

Evidence suggests that time spent in sedentary behaviours can be a key factor in the development of cardiovascular disease9-11, T2DM9,11, the impairment of physical function12 and increased risk of all-cause mortality.9-11,13,14 A recent meta-analysis has highlighted that these links are independent of physical activity levels.15 Data has indicated that adults typically spend 50-70% of their time engaging in sedentary behaviours16, with persons at risk of chronic disease towards the higher end of the scale.17,18 Further to this, higher levels of sedentary time is associated with poorer metabolic profiles in people with T2DM.19 In response to mounting evidence, the 2019 Copenhagen Consensus Statement on physical activity and ageing highlighted the potential dangers associated with sedentary behaviour as an independent risk factor for health in adults and called for further research which explores the benefits of replacing sedentary behaviour with bouts of activity.20

Breaking prolonged sitting and glucose regulation

The detriments of extended periods of sitting on glucose regulation have been previously established21-23 and research has endeavoured to address this in a variety of ways. Studies have most frequently shown the beneficial impact of breaking sitting time with light intensity physical activity24-27, standing25,28, and resistance exercise.27,29 However, some research has also shown a positive impact of performing stretching activities30,31 and upper body activity in a seated position32 in controlling blood glucose levels.

When compared to people who typically engage in prolonged uninterrupted sitting, those who regularly break up sitting time have been shown to have improved cardio-metabolic risk profiles.19,33 Specific populations, based on gender, ethnicity, and BMI have shown to have greater postprandial glucose and insulin responses to interrupting sitting time.34 Further to this, breaking up sitting time with physical activity appears to be more beneficial to those with poorer health profiles. In response to light activity breaks, those with less favourable cardiorespiratory profiles at baseline showed much more positive responses, in relation to glucose regulation, to breaks in sitting time than those with less positive profiles.35

Physical function

Over recent years, impaired physical function has increasingly become a major cause for concern within the diabetic population. A recent analysis of UK Biobank participants found that 13% of people with diabetes also experienced frailty as a comorbidity, and 54.8% were found to have pre-frailty, showing considerable impairment of physical function across the population.36 Diabetes is also associated with increased likelihood for the development of various comorbidities, including: depression, cognitive impairment, ulcers, infections, falls, chronic pain, urinary incontinence, and use of multiple medications.37 All of which can increase the rate of premature ageing and subsequent onset of impaired physical function. Meta-analysis has shown that people with diabetes who also suffer from some form of frailty are considerably more likely to experience hospitalisation or mortality.38 The same study suggests that time spent in sedentary behaviours is a key factor in the impairment of physical function in various populations.

Timing, duration, and frequency

For improvements to metabolic health through breaks in sitting time, different break types, durations, modalities, and intensities may be more appropriate for different populations based on symptoms and habitual physical activity levels.39 Research investigating the timing of physical activity has been growing over recent years, particularly with respect to timing of structured exercise and postprandial metabolic responses. Borror et al.’s review looked at studies which have investigated various timings, durations, intensities, and modalities of exercise and the effects of glucose control in persons with T2DM.40 The studies varied greatly in results, with the most effective outcomes being seen in aerobic type activities and resistance type activities. The consensus from this review appears to suggest that it is important for persons with T2DM to increase energy expenditure following the largest meal of the day. Several studies have shown that postprandial exercise is highly effective at lowering the glycaemic impact of a meal.41-44 In addition to this, there is evidence which has shown that exercise performed before breakfast is effective in increasing fat oxidation over the course of the day and reducing postprandial triglyceride response.45 More recently, a study showed that a 6-week aerobic exercise training programme was more effective in improving appetite control, calorie intake, and weight loss in inactive, overweight women when performed in the morning.46 There is clearly a suggestion that the timing of exercise plays an important role in managing glucose control through exercise. Applying these principles of timing of exercise to a programme designed to reduce sitting time may prove to be more successful than a generic approach.

It has been hypothesised that the effectiveness of any given physical activity bout is highly dependent on the levels of nutrients consumed and that monitoring of Continuous Glucose Monitoring System (CGMS) data may be an effective tool to aid in the prescription of physical activity.47 Continuous monitoring of blood glucose could help to inform the frequency of physical activity bouts to break up sitting time and yield greater improvements in glucose control. Though, some evidence has suggested that there may not be any difference in the benefits of interrupting sitting time with increased frequency when compared to less frequent intrerruptions.48 Another study found similar results, with glucose remaining unchanged regardless of differing frequency of breaks; however, postprandial insulin responses were improved with more frequent breaks.49

Healthy sleep can also play a major role in the deterioration of cardiometabolic health, particularly with respect to glucose control and T2DM.50 There appears to be a “U” shaped relationship between duration of sleep and cardiometabolic risk, with long and short duration sleepers being at increased risk.51 Further to duration of sleep, timing of sleep can impact health status. Chronotypes, typically referred to as morning type, evening type, and intermediate, can be driven by a number of factors including circadian rhythms, occupation, and lifestyle factors.52,53 Individuals with evening chronotypes appear to be at a greater likelihood of engaging in longer durations of activities which typically involve large amounts of sitting.51,54 Wennman and colleagues have previously suggested the use of chronotypes as a method of targeting specific health behaviours such as sitting time.55

Coronavirus (COVID-19)

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), more commonly referred to as COVID-19, emerged towards the latter half of 2019 and is considered to be one of the most serious public health crises in recent history.56 As of 23rd March 2020, the UK has been under stringent restrictions, limiting individuals to leaving their homes only to travel to work where “absolutely necessary”, to shop for essential items, to exercise once a day, and to access medical care.57 This has and will continue for some time to impact on research activities. This protocol details a study that is planned when these restrictions are not in place and participants are able to attend our research centre. However, should restrictions and social distancing remain in place when the study starts, we will implement an alternative research methodology – details of which can be found in Appendix 1. Briefly, Part 1 – Lab-based study would no longer take place and Part 2 – Intervention would be conducted remotely (see Appendix 1 for suggested alternative data collection and intervention delivery methods).

# OBJECTIVES

## 5.1 Primary Objective

Part 1 – Lab-based

To ascertain the types of activities used for breaking sitting time which provide the most favourable affective responses.

Part 2 – Intervention

To investigate whether personalised recommendations for reductions in prolonged sitting time with respect to time and type are more effective than generic advice for improving glucose control over a 4-week intervention.

## 5.2 Secondary Objectives

Part 1 – Lab-based

* To quantify the rate of perceived exertion of different activities used for breaking up prolonged sitting time
* To quantify the energy expenditure of different activities used for breaking up prolonged sitting time
* To quantify degree of muscle activation of different activities used for breaking up prolonged sitting time
* To investigate whether affective responses, perceived exertion, energy expenditure, muscle activation, and the degree of pain observed across different activities used to break up sitting time are associated with baseline measures.

Part 2 – Intervention

* To investigate whether fasting metabolic markers (glucose, insulin, lipid profile) are changed following the intervention.
* To investigate whether variability in blood glucose (weekly average) and time spent in hypo- and hyper-glycaemia change at the end of the intervention as assessed via Continuous Glucose Monitoring System (CGMS).
* To investigate whether physical function is improved following the intervention.
* To investigate changes to overall sedentary behaviour, sleep, and physical activity during and at the end of the intervention.

# STUDY DESIGN

## 6.1 Summary of Trial Design

The RESPONSE study will consist of two parts: Part 1 – a lab-based study to assess the effects of different activities used to break up prolonged sitting time; and Part 2 – a 4-week randomised trial.

Part 1 – Lab-based will involve participants attending the Leicester Diabetes Centre to participate in a 5.5-hour sitting condition. This will be interrupted every 20-minutes with one of 16 different activities. Affective response, Rate of Perceived Exertion (RPE), muscle activation, and energy expenditure will be recorded for each activity break.

Part 2 – Intervention is a 4-week randomised trial and will involve participants being randomised (1:1) to one of two treatments: 1) an intervention to break up prolonged sitting time that is tailored to individuals sleeping patterns, meal timings, activity break type response, and 24-hour blood glucose profiles; 2) a generic intervention to break up prolonged sitting. The study will include 4 visits to the Leicester Diabetes Centre, Leicester General Hospital.

Visit 1 (week 1): Screening and baseline data collection, including 8-day accelerometer and CGMS monitoring.

Visit 2 (week 3): Assessment of individuals responses to activity break regimes prior to randomisation (Part 1 – Lab-based)

Visit 3 (week 7): Follow-up placement of accelerometers and CGMS

Visit 4 (week 8): Follow-up clinical data collection after Part 2 – Intervention

## 6.2 Primary and Secondary Endpoints/Outcome Measures

Part 1 – lab-based

The primary outcome of the lab-based study is the quantification affective responses to different activities used to break prolonged sitting time via the feelings scale.

Part 2 – Intervention

The primary outcome measure of this intervention is postprandial glucose excursions assessed via CGMS worn in free living conditions.

**Secondary Outcomes**

Part 1 – Lab-based

The secondary outcomes for the lab-based study are:

* The rate of perceived exertion of different activities used for breaking up prolonged sitting time
* The energy expenditure of different activities used for breaking up prolonged sitting time
* The degree of muscle activation of different activities used for breaking up prolonged sitting time

Part 2 – Intervention

The secondary outcomes in the intervention are:

* Glucose variability (% and standard deviation), average blood glucose, time in range, time above range, time below range, high blood glucose index, low blood glucose index, number of hyperglycaemic episodes, and number of hypoglycaemic episodes derived from CGMS
* AUC for postprandial glucose, insulin, triglycerides derived from the mixed meal challenge
* Fasting glucose, insulin, triglycerides, and full lipid profile.
* Physical function.
* Adherence to regular light upright movement breaks, sedentary time (total and time spent in prolonged sitting), sleep duration and physical activity (total, and time spent in light, moderate and vigorous physical activity). All measured objectively via accelerometery.

**Part 2 – Intervention (PST-INT)**

**Part 2 – Intervention (GST-CON)**

Recruitment of people (with T2DM on mono- or dual-therapy) from primary and secondary care, previous studies within which participants have agreed to be contact for future studies, and diabetes databases and registries.

***Week 0 – Screening (Telephone)***

* Review of basic eligibility criteria
* Explanation of study procedures

***Visit 2; Week 3 – Part 1 – Lab-based***

* 5.5-hour interrupted sitting
* Perform 16 different activities to break sitting time at 20-minute intervals

***Visit 4; Week 8 – Follow-up Assessments following Part 2 – Intervention (Identical to Visit 1)***

* Written, informed consent
* Anthropometrics
* BP/HR
* Bloods (HbA1c, Lipid profile, glucose, insulin)
* Resting Metabolic Rate

***Visit 1; Week 1 – Baseline Assessments***

8-day monitoring (starting at baseline visit) with activPAL, GENEActiv, and CGMS.

***Visit 3; Week 7 – Monitoring with accelerometers and CGMS***

* Repeat free living measurements during final 8-days of intervention period

*Weekly 1-2-1 (telephone or in person) review with research team*

LDC: Leicester Diabetes Centre; HGS: Handgrip strength; CGMS: continuous glucose monitoring system; SPPB: short physical performance battery; HbA1c: glycated haemoglobin; PST-INT: personalised sitting time intervention; GST-CON: generic sitting time control

*Generic recommendations.*

*Personalised recommendations based on sleep patterns, meal timings, break type response, and 24-hour blood glucose profile.*

* Response to a mixed meal challenge
* Questionnaires (WHO-DAS, Sarc-F, EQ-5D-5L, mMRC Dyspnoea, HADS, UKDDQ, MEQ, NMQ, CFQ-11)
* Functional tests (HGS, SPPB, mPPT, ISWT)
* Familiarisation with Visit 2 procedures

Randomisation 1:1, stratified by sex

**Figure 1. Trial Schematic**

**Table 1. Gantt chart representing predicted timelines for study**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Phases** | **Weeks** | | | | | | | | |
| **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** |
| **Baseline Assessment** |  |  |  |  |  |  |  |  |
| **Free-living Assessment** |  |  |  |  |  |  |  |  |
| **Part 1 – Lab-based** |  |  |  |  |  |  |  |  |
| **Part 2 – Intervention** |  |  |  |  |  |  |  |  |
| **Free-living Assessment** |  |  |  |  |  |  |  |  |
| **Follow-up Assessment** |  |  |  |  |  |  |  |  |

# TRIAL PARTICIPANTS

## 7.1 Overall Description of Trial Participants

People with a diagnosis of T2DM receiving mono- or dual-therapy with HbA1c of 6.5-9%.

## 7.2 Recruitment strategy

Recruitment will target individuals via multiple settings, general practice/primary care, research databases (Leicester Diabetes Centre), through the community/internet and pharmacies

**Recruitment from general practice and primary care**

The recruitment phase will commence as soon as ethical, research governance, and regulatory approval has been granted and the Sponsor green light has been provided.

GP surgeries will be contacted, requesting support in recruitment for this study. They will be asked to circulate participant invitation letters (PIL) and participant information sheet (PIS), along with a reply slip with a pre-paid envelope that can be returned to the research team. Access to GP surgeries will be supported by the CRN. Other primary care centres within University Hospitals Leicester NHS trust will also be asked to display advertisement material and circulate PIL and PIS to potential participants.

**Recruitment through participant and volunteer databases**

The Leicester Diabetes Centre has access to a rich source of datasets containing individuals who have consented to be informed of and invited to future research studies. This includes approximately 1000 individuals with T2DM who have completed the CODEC study; these individuals were rigorously phenotyped for medication usage and physical function. Other completed studies and databases also have diabetes status coded and will be used for recruitment.

Leicester Diabetes Centre also has a volunteer database of people with T2DM who have given consent to be contacted about future research. We will also utilise these databases.

**Community and Internet**

Community and internet: Individuals will be recruited from the general public through the use of NHS Trust websites (www.leicesterdiabetescentre.org.uk and www.leicestershospitals.nhs.uk) and other relevant websites ([www.nihr.ac.uk](http://www.nihr.ac.uk), www.twitter.com), which will have links to the PIL and PIS. If they are interested in taking part, they can return the form on the PIS and send it back to the research team using a pre-paid envelope. Advertisement material will also be distributed to community centres and will be asked to display study material. The research team will also contact local media organisations and community organisations to outline the study and arrange visits from a member of the research team

**Pharmacies and Hospital Clinics**

Local pharmacists and relevant hospital clinics within UHL will be asked if they are willing to display the study poster in their establishment. The poster will contain contact information for the study team that the individual can contact if they are interested in taking part in the study. Pharmacists will not recruit participants and will only display the poster and leaflets for the study. Clinicians may identify participants and distribute PIS and leaflets.

## 

## 7.3 Inclusion Criteria\*

**Table 2. Inclusion criteria for study population**

|  |
| --- |
| Inclusion Criteria |
| 1. Men and women 2. Age 40 to 75 years, inclusive 3. Diagnosed with T2DM within the last 5 years 4. Diabetes controlled by diet alone, or receiving mono- or dual-therapy 5. No changes to glucose lowering medication regime within the preceding 3 months 6. HbA1c levels 6.5-9% 7. Able and willing to give informed consent 8. Able to understand spoken and written English 9. Able to undertake light physical activity 10. Weight stable; ≤ 3kg weight change in preceding 3 months 11. Willingness and availability to participate in the proposed intervention |

## 7.4 Exclusion Criteria\*

**Table 3. Exclusion criteria for study population**

The participant may not enter the study if ANY of the following apply:

|  |
| --- |
| Exclusion Criteria |
| 1. Type 1, gestational, or monogenic diabetes mellitus 2. On insulin therapy 3. Changes to glucose lowering medication regime within the preceding 3 months 4. Hospital admission in preceding 3 months 5. Current or planned pregnancy or breast feeding 6. Contra-indications to exercise 7. Participation in another research study with investigational medical product in the preceding 3 months 8. Currently participating in a structured exercise programme 9. Serious illness with life expectancy < 1 year 10. Individuals with history of chronic pancreatitis 11. Previous major amputation 12. Recent cardiovascular event (within 12 months) 13. Steroid use 14. Comorbidity that the research team consider to be a contraindication to involvement in the study 15. Unable to communicate in English 16. Unable to provide written informed consent 17. Diabetic foot ulcers, gangrene 18. Recent diagnosis or treatment for cancer (within 12 months) |

\*In the circumstance that an individual is not sure whether they meet the inclusion/exclusion criteria, they will be reviewed by a named doctor on the delegation of authority log for a clinical decision to be made during the baseline visit.

# STUDY PROCEDURES

## 8.1 Informed Consent

Before any ethically approved study related procedure can take place, the participant must complete the latest approved version of the informed consent form. Participant information with full details of procedures, expectations, potential risks and withdrawal rights will be provided to the participants a minimum of 24 hours prior to their first study appointment to give them adequate time to read through it. It will then be presented both in writing and verbally at the first study appointment prior to consent being taken. 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, and with no obligation to give the reason for withdrawal. If a participant withdraws from the study but does not withdraw their consent, then data already obtained may be used for the study. This will be made clear on the PIS and consent form. If a participant has withdrawn due to an adverse event, a medic will follow-up as appropriate.

Consent will be received by someone who has received generic consent training and has been authorised by the Chief Investigator to do so, they will also be included in the delegation of authority log. The original signed form will be retained at the study site within the TMF and a copy will be given to the participant.

## 8.2 Screening and Eligibility Assessment

Prior to commencing the study, participants will be contacted via telephone for an initial screening to assess eligibility. Following this, potentially eligible participants will be invited to visit the Leicester Diabetes Centre in a fasted state for a baseline/screening/familiarisation visit. Part of the purpose of this visit is to explain the study and provide participants the opportunity to ask any questions they may have. Once this has been completed and the participant has decided to take part, informed consent will be sought, eligibility will be checked, and once confirmed, baseline measurements will be taken.

## 8.3 Baseline Assessments

Once eligibility has been confirmed, baseline measurements will be taken. These are described here and outlined in Figure 2.

**Baseline Characteristics (Visit 1)**

Medical History and Anthropometrics

Participants will complete a health questionnaire including their DOB, gender, and ethnicity according to SOPs and medical history will be provided. Various routine anthropometric, demographic, and clinical measurements will be collected (detailed below). Anthropometric measures of body composition (total body fat and fat-free mass via bio-impedance assessment (Tanita TBE 611: Tanita, West Drayton, UK)), weight, height and waist circumference (midpoint between the lower costal margin and iliac crest) will be recorded, to the nearest 0.5%, 0.1kg, 0.5cm and 0.5cm respectively, according to SOPs.58

Resting Metabolic Rate

Indirect calorimetry will be used to assess RMR according to SOPs. RMR will be measured using a ventilated hood system at Leicester Diabetes Centre, where participants will be asked to lie in a supine position and instructed to relax, remain awake and be still. The hood will be placed over the participant’s head to enable the measurement of all expired gases over a predetermined time period according to SOPs. RMR will be assessed following an overnight fast.

Blood Profile

Arterial blood pressure and resting HR will also be measured in the sitting position; three measurements will be obtained and the average of the last two measurements will be used. A fasted blood sample will be taken via venepuncture, according to SOPs, for assessment of HbA1c, fasted glucose, fasted insulin, and lipid profile (HDL, LDL, and total cholesterol).

Response to a Mixed Meal Challenge

Participants will be asked to consume a standard mixed meal providing 8 Kcal per kg of bodyweight and consisting of ~13% protein, ~52% carbohydrate, and ~35% fat. Blood samples will be collected at fasting baseline, then 15, 30, 45, 60, 90, 120, 150, and 180 minutes following meal stimulation. Samples will be processed and stored according to relevant SOPs. The samples will be analysed to measure glucose, c-peptide, insulin, and glucagon levels.

Questionnaires

Functional capacity/disability (WHO Disability Assessment Schedule59, The Sarc-F Questionnaire60), quality of life (EQ-5D-5L61), breathlessness (modified Medical Research Council dyspnoea scale62), anxiety/depression (Hospital Anxiety and Depression Scale63), chronotype (Morning-Evening Questionnaire64), chronic pain (Nordic Musculoskeletal Questionnaire65), fatigue (Chalder Fatigue Scale66), and dietary intake (United Kingdom Diabetes and Diet Questionnaire67) will be assessed using self-report questionnaires.

Hand grip strength (HGS)

HGS is measured using a digital handheld dynamometer three times on each side, with the elbow flexed at a right angle and the forearm in neutral position. The maximum of the readings generated is taken as the maximum grip strength.

Short Physical Performance Battery (SPPB)

The SPPB measures balance, gait speed, and ability to stand from a chair and has been shown to measure the risk of disability and mortality.68 It comprises of the tests outlined below which collectively take approximately 15 minutes to complete;

*Chair stands*: The participant will start from a seated position on a hard, upright chair (such as a dining chair), with the feet flat on the floor and the knees bent at 90°. For the test, the time taken for the participant to stand up fully and then return to sitting, without using the hands 5 times is measured.

*Standing balance*: Tests in three progressive positions. If the participant can complete 10 seconds in the specified position, then the starting position is progressed to the next stage:

* Feet together
* Semi-tandem
* Tandem

*Gait speed*: The time taken for the participant to walk 4m on a level course. It is measured a second time after a short break.

Modified Physical Performance Test (mPPT)

The mPPT includes seven standardised tasks: walking 50ft, putting on and removing a coat, picking up a penny, standing up from a chair, lifting a book, climbing one flight of stairs, and safely turning 360°. The score for each task ranges from 0 to 4; a perfect score is 36.69 mPPT has previously been shown to correlate well with various factors relating to impaired physical function.

Incremental Shuttle Walk Test (ISWT)

The ISWT has previously been validated against VO2 max and VO2 peak in clinical populations70 and as a measure of physical function.71 Participants will perform the ISWT to assess VO2 max and physical function through walking ability. The test involves participants walking consecutive 10-metre shuttles in consistent time with an audible beep. This beep will become progressively faster until the participant is no longer able to maintain the pace. Participants will be taken through a short practice session to minimise the impact of learning effects. The total number of shuttles performed will be recorded by the research team.72

Familiarisation

Participants will also be taken through a brief familiarisation to ensure that they are competent in all the activity break types which will be used in the second visit.

Physical Activity Monitoring and Continuous Glucose Monitoring System (CGMS)

At the end of the first visit, participants will be asked to wear a wrist worn accelerometer 24hours/day for up to 8-days on their non-dominant wrist. The participant does not have to do anything with the device apart from wear it and once it is fitted on the day of the appointment, it will not need to be removed until the wear period is over.

Participants will also be asked to wear the activPAL device to assess time spent sitting, standing, stepping, and transitions between these postures. The activPAL has been shown to be highly accurate in measuring these behaviours.73 They will wear the device 24hours/day for up to 8-days on their thigh. The device will be initialised using the manufactures software under default settings. Waterproofing of the device will be achieved using a nitrile sleeve and Hypafix dressing. Alongside this, participants will fill out a wake and sleep log for the days they wear the devices and record any time when the devices are removed.

The CGMS will assess the following based on standardised recommendations74:

* Glucose variability (%CV and standard deviation)
* Postprandial glucose excursions (primary outcome)
* Mean glucose concentrations
* Estimated HbA1c
* Time in range (3.9 – 10 mmol/L)
* Time above range (> 10 mmol/L)
* Time below range (< 3.9 mmol/L)
* Number of hyperglycaemic episodes (15 minutes or more)
* Number of Hypoglycaemic episodes (15 minutes of more)
* High blood glucose index
* Low blood glucose index

In addition, the number of days the CGMS device is worn and the percentage time the CGMS is active will be derived. The CGMS will be worn on the participant’s arm following baseline and between the post-intervention measurement days. The CGMS will be worn for a minimum of 8-days. Analysis will exclude at least the first 24 hours of wear to minimise any carry over effect from the measurement condition. This will allow for comparison from the baseline to the end of the intervention.

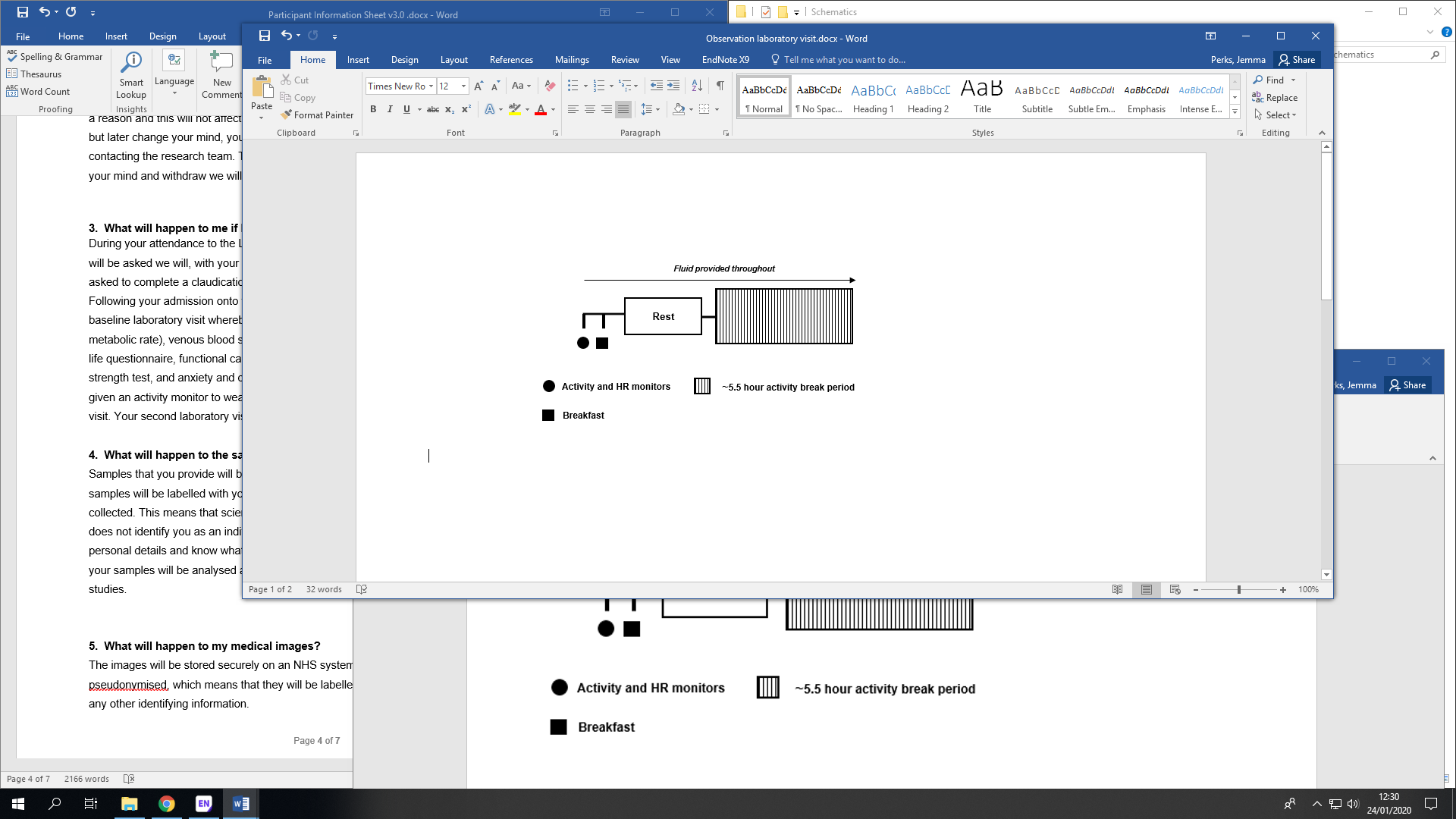
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**Figure 2.** **Schematic of the baseline laboratory visit procedures.**

**Part 1 – Lab-based (Visit 2)**

For Part 1 – Lab-based, participants will arrive at the laboratory in a fasted state. Upon arrival at the study centre, before commencement of the observation, participants will return the activity monitors issued to them for the free-living period and will be fitted with new activity monitors and heart rate monitors (Polar Team 2 system: Polar, Electro Oy, Kempele, Finland) to be worn for the duration of the visit. CGMS will not be changed and will continue to be worn throughout the testing day. Participants will then be given a standardised breakfast which replicates the breakfast that they were given at the baseline testing day. Participants will also be given a standardised snack part way through the 5.5-hour period. The participants will then be given electrode embedded clothing to monitor muscle activation for the duration of the observation.



**Figure 3. Schematic of Part 1 – Lab-based visit procedures.**

Participants will engage in a 5.5-hour period of sitting, with 2-minute activity breaks occurring every 20-minutes. The activities will include:

1. standing; 2) self-paced walking; 3) two footed tip toe balance; 4) mini squats; 5) self-paced arm ergometry while seated; 6) standing calf stretch; 7) resistance band biceps curls while seated; 8) wall press-ups; 9) sideways leg lifts; 10) chest stretch; 11) step-ups; 12) back stretch; 13) single-leg balance; 14) standing hamstring stretch; 15) resistance ball squeezing (with hands) while seated; 16) heel taps while seated.

Activities will be grouped into one of four activity types: 1) Movement-type Activities (arm ergometry, step-up, walking, heel taps); 2) Resistance-type Activities (wall press-up, biceps curl, mini squat, resistance ball squeezing); 3) Stretching-type Activities (chest stretch, back stretch, hamstring stretch, calf stretch); and 4) Balancing-type Activities (standing, single leg balance, sideways leg lift, two footed tip toe balance) (Figure 3). Participants will complete activities from each group at random, and each group type will be randomised until all the activities have been completed by each participant. Before the activity begins, participants will be shown a card with details of how to perform each activity and given a live demonstration by a member of the research team. If required, the demonstrator will complete the activities with the participant. In the final 30-seconds of each break in sitting, participants will be asked to rate their perceived exertion on the Borg RPE scale, affective response on the feeling scale, and acute pain on the Borg CR10 scale. Lower body muscle activation will be monitored for the duration of the period using electrode embedded clothing. Respiratory exchange ratio, fat and carbohydrate oxidation rates, and metabolic rate will be monitored through indirect calorimetry during each bout of activity.

Figure 4. Randomisation of activity types

Measures

**Feeling Scale**

Rejeski and colleagues developed a bipolar scale which ranges from -5 very bad to +5 very good. The feeling scale measure affect/ mood which can be used while participating in exercise.75 Some individuals find exercise pleasurable, whereas others find it to be unpleasant. Feelings may also fluctuate over time and by exercise type. Within the last 30 seconds of each activity break, participants will be asked to rate their feelings on the feeling scale.

**Rate of Perceived Exertion**

Borg’s rating of perceived exertion scale is a 15-grade scale (6-20), which ranges from very, very light to very, very hard. Perception of exertion during physical work indicates physical strain and allows for the quantification of subjective symptoms during exercise. RPE increases linearly with exercise intensity, the same way oxygen consumption and heart rate increase linearly with work load and gives insight into how subjective symptoms relate to objective findings.76 Within the last 30 seconds of each activity break, participants will be asked to rate their perceived exertion on the Borg scale.

**Acute Pain**

The Borg CR1077 (0 no pain - 10▪ absolute maximal pain) will be used by participants to grade the amount of pain they experience during each break in sitting time. Within the last 30 seconds of each break, participants will be asked to rate their pain on the scale.

**Muscle Activation**

Where capacity allows, assessment of muscle activation will be conducted through the use of “smart shorts”. The use of smart shorts to assess muscle activity during exercise, physical activity, and sedentary behaviour in lab and free-living conditions has been done previously. Validation studies have shown the use of electrode embedded clothing to be an effective measure of electromyography (EMG) activity.78 Researchers have used this technology to assess muscle activity in both activity79 and inactivity80, solidifying their use as a valid and reliable alternative to traditional laboratory-based assessment methods .

**Gas Analysis**

Respiratory Exchange Ratio (RER) and metabolic rate (*V̇*O2) will be monitored using indirect calorimetry for the duration of each physical activity break and a short period preceding each break. The mask will be fitted 5-minutes before the commencement of each break to minimise disruption to the participant’s normal breathing pattern and will be removed after completion of the break. Metabolic data will be reported as 1) the standardised metabolic equivalent of each activity (METstandard) defined as the average *V̇*O2 (ml/min.kg) during the activity divided by 3.5 and 2) the relative metabolic equivalent of each activity (METrelative) defined as the average *V̇*O2 (ml/min.kg) during the activity divided by resting *V̇*O2, RER will also be reported.

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**Figure 5. Schematic of 5.5-hour sitting breaks procedure**

**Part 2 – Intervention: Follow-up Assessments (Visit 4)**

The follow-up assessment visit will be a replication of the first visit (baseline) according to the outcome assessment schedule (see Table 4), with the exception of the accelerometers and CGMS. Assessments will be anthropometrics, RMR, blood profile, response to a mixed meal challenge, all questionnaires, HGS, SPPB, mPPT, and ISWT.

## 8.4 Randomisation

This study has 2 randomisation elements. To determine the order of assessment activities during the 5.5-hour sitting condition in Part 1 – Lab-based and to determine allocation into different arms of Part 2 – Intervention.

Part 1 – Lab-based: Activity Order (visit 2)

Activity break types and activities will be randomised and performed in a cycle until all 16 activities have been completed. Randomisation will be conducted by a statistician.

Part 2 – Intervention: Intervention Allocation

Participant numbers will be assigned sequentially as each participant enters the study. The participants will be assigned to a measurement condition order through a randomisation schedule based on the randomisation plan, stratified by sex. Randomisation will be conducted by a statistician. The two experimental conditions A (generic advice for breaking up sitting time) and B (personalised advice for breaking up sitting time) will not be blinded as this is not possible as the conditions require the participant to alter their behaviour. Participants will be contacted by telephone to make them aware of their group allocation.

## 8.5 Subsequent Assessments

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Measure** | **Method** | **Outcome** | **Measurements at each time point (contact)** | | | |
| **Visit 1** | **Visit 2** | **During Intervention** | **Visit 4** |
| Biochemical Analysis | Cannulated vein | HbA1C | x |  |  | x |
| Fasted Glucose | x |  |  | x |
| Fasted Triglycerides | x |  |  | x |
| Fasted Insulin | x |  |  | x |
| Lipid Profile | x |  |  | x |
| CGMS | Blood Glucose | x | x | X |  |
| Indirect Calorimetry | RER and Metabolic Rate |  | x |  |  |
| Ventilator Hood | RMR | X |  |  | x |
| Automated BPM | Blood Pressure | x | x |  | x |
| Accelerometers |  | Sedentary Behaviour | x | x | x\* |  |
| Physical Activity | x | x | X |  |
| Sleep Patterns | x | x | x\* |  |
| Questionnaires | WHO-DAS | Functional Capacity/Disability | x |  |  | x |
| Sarc-F | Functional Capacity/Disability | x |  |  | x |
| HADS | Anxiety/Depression | x |  |  | x |
| mMRC Dyspnoea Scale | Breathlessness | x |  |  | x |
| UKDDQ | Dietary Intake | x |  |  | x |
| CFQ-11 | Fatigue |  |  |  |  |
| EQ-5D-5L | Quality of Life | x |  |  | x |
| MEQ | Chronotype | x |  |  | x |
| NMQ | Chronic Pain | x |  |  | x |
| Feeling Scale | Affective Response to Breaks |  | x |  |  |
| Borg RPE Scale | Physical Exertion during Breaks |  | x |  |  |
| Borg CR10 Scale | Acute Pain |  | x |  |  |
| Anthropometrics |  | Height | x |  |  |  |
|  | Weight | x | x | X | x |
|  | Waist Circumference | x | x | X | x |
| BIA | Body Fat Percentage | x | x | X | x |
| Physical Function | SPPB | Physical Function | x |  |  | x |
| MPPB | Physical Function |  |  |  |  |
| Shuttle Walk Test | Usual Walking Speed | x |  |  | x |
| Dynamometer | Hand and Forearm Strength | x |  |  | x |
| EMG (optional) | Muscle Activation |  | x |  |  |
| Glucose Control |  | Response to a Mixed Meal Challenge | x |  |  | x |

**Table 4. Trial Procedures**

\* Sedentary behavior and sleep patterns will only be directly assessed during the final 7-days of the intervention when participants are wearing the activPAL device.

## 8.6 Definition of End of Trial

The end of trial is the date that all secondary outcomes have been analysed.

## 8.7 Discontinuation/Withdrawal of Participants from Study Treatment

Each participant has the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

* Consent withdrawn
* Safety
* Significant non-compliance with intervention regimen or study requirements (failing to meet a 30-minute reduction in sitting time per day as per the activity monitor data)
* Clinical reasons
* Ineligibility (either arising during the study or retrospective having been overlooked at screening)
* Significant protocol deviation

The reason for withdrawal will be recorded in the CRF. However, participants will not need to provide a reason for their withdrawal if they do not wish not to do so. Any data collected up to the point of consent withdrawal will be included in the final per-protocol analysis.

## 8.8 Source Data

Source documents are original documents, data, and records from which participants’ CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). In this study the CRF will be used as the source document for the data collection and analysis.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

# TREATMENT OF TRIAL PARTICIPANTS

## 9.1 Description of Study Treatment

Overall, participants will be required to visit the Leicester Diabetes Centre, Leicester General Hospital, four times. Prior to visiting the lab, participants will be requested to avoid alcohol, caffeinated drinks, and exercise 48 hours prior to the measurement day, while vigorous intensity physical activity should be avoided 72 hours prior. This is because evidence suggests a single bout of exercise may affect glucose tolerance and insulin sensitivity for up to 48 hours, while insulin sensitivity may be affected up to 72 hours post strenuous exercise. From 10 pm onwards the night before the visit, the participants will be required to fast, except for drinking water.

**Part 1 – Lab-based**

This will be based at Leicester Diabetes Centre. In order to minimise movement during the 5.5-hour sitting condition, participants will be brought water upon request. Toilet breaks will be taken ad libitum, and study staff will escort the participant in a wheelchair to minimise movement.

**Part 2 – Intervention**

Intervention 1 (personalised)

The personalised intervention will be in free living conditions with the aim of reducing prolonged sitting time at targeted times using targeted activities. Guidance will be based on overall patterns of sedentary behaviour, chronotype, postprandial responses, and metabolic and affective responses to the activity breaks performed during Visit 2 (see table 5.). Participants will be encouraged to reduce prolonged sitting time by at least 30-minutes per day. The prioritisation of the different strategies used for breaking up sitting time will be decided by the study team based on each participant’s data in order to maximise the potential effectiveness. For example, if a participant shows a strong reaction to a particular break type then it may be prioritised; or if the participant has especially large spikes in blood glucose at specific times of the day, then activities will be targeted around that time.

**Table 5. Strategies for intervention personalisation**

|  |  |
| --- | --- |
| Types of breaks | Those that produce the most positive affective or metabolic responses (derived from Part 1. Lab-based study) will be prioritised |
| Overall pattern of physical activity | Intervention breaks will be targeted at the most sedentary parts of the day; specifically, the times of day that prolonged bouts of sedentary time typically occur |
| Meal patterns and CGMS | The routine timing of the meal that is causing the largest elevation in postprandial glucose will be identified, with breaks specifically targeted in the early postprandial phase |
| Chronotype | Intervention breaks will be tailored to individual chronotypes, with morning chronotypes having an intervention that is shifted earlier on in the day than those with an evening chronotype. Evening chronotypes will also help identify individuals at high risk of prolonged sedentary behaviour, with strategies implemented to specifically target them. |

Participants will be asked to maintain their usual diet.

Participants will have one face-to-face educational and instructional session before commencement. The purpose of this session is to explain the times, frequencies, durations, and types of activities in which the participant should engage. The session will also include guidance on how to self-monitor their sitting time. We know from previous research that a one size fits all approach to a self-monitoring/prompt tool does not work. Therefore, participants will be given a choice from a selection of tools to self-monitor their sitting time and activity and/or provide prompts to break up sitting. Each of these tools will be commercially available and will range from consumer wearable devices, phone apps and computer applications. For example, one option of a wearable device may be a Fitbit, which vibrates if the wearer has not done enough steps in that hour, one option for a phone app may be Chairless which gives notifications for long sitting bouts and one option for a computer application may be workrave where the user can set up reminders every 30 minutes (or whatever the user chooses) to break up their sitting.

Participants will receive telephone/face-to-face (depending on preference) feedback from the research team at least once per week. These sessions will review the data from the preceding week and provide the participants with guidance, positives and negatives of previous days sitting time, and any adjustments which may need to be made.

Intervention 2 (generic)

The generic intervention will be in free living conditions with the aim of reducing prolonged sitting using generic advice. Guidance will be minimal, will be standardised, and will not be informed by any of the personal data collected in the previous visits. Participants will be encouraged to reduce prolonged sitting time by at least 30-minutes per day. Participants will choose freely when and how they break up their sitting time.

Participants will be asked to maintain their usual diet.

Participants will have one face-to-face educational and instructional session before commencement. The purpose of this session is to ensure that they have the knowledge and materials required to reduce their sitting time. The session will also include guidance on how to self-monitor their sitting time. Participants will be given the same options of devices as those offered to the personalised intervention group throughout the intervention to aid them in managing their sitting time.

Participants will receive telephone/face-to-face (depending on preference) feedback from the research team at least once per week. These sessions will review the accelerometer data from the preceding week and provide the participants with guidance, positives and negatives of previous days sitting time, and any adjustments which may need to be made (without reference to data collected in previous visits).

## 9.2 Storage of Study Equipment or Related apparatus

Study equipment will be stored at the Leicester Diabetes Centre, Leicester General Hospital and at the University of Leicester Academic Unit, Leicester General Hospital.

## 9.3 Compliance with Study Treatment

Compliance to the conditions in Part 2- Intervention will be measured throughout regular telephone contact with the participants. A member of the study team will contact participants at least once per week to promote compliance with the study treatment.

# SAFETY REPORTING

## 10.1 Definitions

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### 10.1.1 Adverse Event (AE)

An AE or adverse experience is:

Any untoward medical occurrence in a patient or clinical investigation participants, which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the study, whether considered related to the study.

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### 10.1.2 Adverse Reaction (AR)

All untoward and unintended responses related to the study.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study qualify as adverse reactions. There are no expected ARs in this study.

### 10.1.3 Severe Adverse Events

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

### 10.1.4 Serious Adverse Event or Serious Adverse Reaction

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

* Results in death,
* Is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

* Requires inpatient hospitalisation or prolongation of existing hospitalisation,
* Results in persistent or significant disability/incapacity, or
* Is a congenital anomaly/birth defect.
* Other important medical events\*

\*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant andmay require medical or surgical intervention to prevent one of the outcomes listed above.

### 10.1.5 Expected Serious Adverse Events/Reactions

This study is a non-invasive lifestyle modification study, therefore no SAE/Rs are expected.

### 10.1.6 Suspected Unexpected Serious Adverse Reactions

This study is a non-invasive lifestyle modification study, therefore no SUSARs are expected.

## 10.2 Reporting Procedures for All Adverse Events

All AEs occurring during the study observed by the investigator or reported by the participant, whether attributed to study, will be recorded on the CRF. The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to study, other suspect device and action taken. Follow-up information should be provided as necessary.

AEs considered related to the study as judged by a medically qualified investigator or the sponsor will be followed until resolution or the event is considered stable. All related AEs that result in a participant’s withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

## 10.3 Reporting Procedures for Serious Adverse Events

All SAEs must be reported to the Sponsor within one working day of discovery or notification of the event. The Sponsor will perform an initial check of the information and ensure that it is reviewed at the next R&D Management meeting. All SAE information must be recorded on an SAE form and sent to the Sponsor using the appropriate reporting form and the contact details on there. Additional information received for a case (follow-up or corrections to the original case) needs to be detailed on a new SAE form which must be sent to the Sponsor using the appropriate reporting form and the contact details on there.

The Sponsor will report all SUSARs to the Research Ethics Committee concerned. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The CI will inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

In addition to the expedited reporting above, the CI shall submit once a year throughout the study or on request an Annual Report to the Ethics Committee which lists all SAEs / SUSARs that have occurred during the preceding 12 months.

# STATISTICS

## 11.1 Description of Statistical Methods

Data gathered Part 1 – Lab-based

Data generated from Visit 2 is not aimed at testing a specific hypothesis, formal hypothesis testing for each activity will not be undertaken. Data for each activity will be reported as mean (95% CI). Non-parametric data will be reported as median (95% CI). In order to quantify the degree of similarity between activities, each activity will be compared to walking, the most common form of physical activity used in exercise intervention in T2DM. To achieve this, pairwise 95% equivalence tests will be used to determine whether the 95% CI for the mean/median of each activity falls within the proposed equivalence zone for walking. Equivalence zones will be defined as ± 1 unit for the RPE and Feeling Scale or ± 10% of the mean/median of the walking activity for all other outcomes. Finally, post-hoc generalised estimating equation modelling will be undertaken to investigate whether collected participant characteristics are associated with selected pooled outcome data (RPE, Feeling Scale, heart rate, muscle activation, and METrelative). This will help define which participant characteristics may be predictive of psychological and physiological responses to the physical activity breaks and hence which individuals may need enhanced support in future interventions. Repeated measures will be considered using an exchangeable correlation matrix and an appropriate link function will be selected for the data distribution.

Data gathered from Part 2 – Intervention

Data will be analysed using generalised estimating equations considering repeated measures using an exchangeable correlation matrix. The primary analysis will be the within group change from baseline reported for each condition separately. Should either group demonstrate a significant change from baseline, between group difference in change will be assessed with a time x condition interaction. Normally distributed data will be analysed using a normal destitution and identity link. Non-normally distributed data will be analysed using a data distribution and link function that produces the best model fit. P<0.05 will be considered significant and data reported as mean (95% CI). Models will be adjusted for sex. In addition, CGMS variables will also be adjusted for percentage of time the device is active. CGMS data will be analysed as both aggregated (overall average values) and disaggregated daily values. Aggregated data will be analysed through a generalised linear model, with daily values analysed using generalised estimating equations, with an unstructured correlation matrix used to account for repeated measures.

## 11.2 The Number of Participants

Part 1 – Lab-based

A sample size of 20 will allow for a 95% CI width (upper value minus lower value) of 1.8 RPE, 1.2 for the feeling scale, and 0.4 for METstandard and METrelative to be generated in the data collected at Visit 2. This is based on previous lab-based data from our group. We anticipate a within-activity standard deviation of 2 points on the Borg RPE scale (ranging from 6 [rest] to 20 [maximal effort]), 1.3 points for Feeling Scale (10 point scale ranging from -5 [very bad] to 5 [very good]), 0.5 for METstandard, and 0.5 for METrelative.81

Part 2 - Intervention

For the randomised trial, assuming an average 24-hour blood glucose level of 8 mmol/L, and that the intervention will reduce these levels by at least 10% (0.8 mmol/L)81 and that the SD of change from baseline is 0.8 mmol/L with a within person correlation of 0.5, we need 10 individuals per group to complete the trial (20 individuals in total). In order to allow for a 20% drop-out, we will recruit 25 individuals.

## 11.3 The Level of Statistical Significance

Statistical analyses tests will be two-sided with a 5% significance level.

## 11.4 Criteria for the Termination of the Trial.

There are no official criteria for trial termination. The trial will be conducted in accordance to the sponsors SOPs and in accordance to the HRA.

## 11.5 Procedure for Accounting for Missing, Unused, and Spurious Data.

Assessment of the primary outcome and secondary outcomes will be assessed on a complete case basis for each activity. Spurious data will be identified based on that judged to be outside the range of physiological plausibility or as 4 standard deviations from the mean.

## 

## 11.6 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviation(s) from the original statistical plan will be described and justified in protocol and/or in the final report, as appropriate.

## 11.7 Inclusion in Analysis

All analysis will be conducted as outline in section 9.3 and 11.5.

# DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

# QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

University of Leicester as sponsor operate a risk-based audit programme to which this study will be subject. The Leicester Biomedical Research Centre (BRC) team will be responsible for all elements of study management on an on-going basis. A documented monitoring log and audit trail will be maintained throughout the lifetime of the study. The Chief Investigator and study co-ordinator will oversee the set-up of and conduct of study procedures at each site. All source data, study documents will be made available for Sponsor monitoring, and any external audits and inspections as appropriate, for example by the Research Ethics Committee.

# CODES OF PRACTICE AND REGULATIONS

## 14.1 Ethics

Approval from University of Leicester (sponsor), London – Bromley REC, the Health Research Authority (HRA) and University Hospitals of Leicester NHS Trust R&D will be sought prior to the commencement of the research. This will ensure that all ethical and indemnity issues are dealt with. The research protocol, participant invitation letter, ICF, participant information sheet and any proposed advertising material will be submitted to the sponsor, main REC, and host institutions for approval. The Study Co-ordinator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents. The Chief Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the International Conference on Harmonisation Guidelines for Good Clinical Practice.

Participants will be free to withdraw at any time from the study without giving a reason and without their legal rights being affected. We do not anticipate any harm, discomfort or risk to any participant enrolled in this study. The overall care and comfort of the participant will always be considered paramount during the study.

## 14.2 Sponsor Standard Operating Procedures

All relevant Sponsor SOPs (UoL and LDC) will be followed to ensure that this study complies with all relevant legislation and guidelines.

## 14.3 Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

## 14.4 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

## 14.5 Approvals

Once Sponsor authorisation has been confirmed, the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted as part of the central Integrated Research Application System (IRAS). The appropriate REC will be notified and regulatory authorities, (HRA in the UK), and the host institution for written approval.

Once Sponsor authorisation has been confirmed, the Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

## 14.6 Participant Confidentiality

The trial staff will ensure that the participants’ anonymity is maintained. The participants will be identified only by initials and a participant’s ID number allocated after full consent has been taken. The participant ID will then be used on all study documentation and electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. Direct access to all documents will be granted where appropriate to authorised representatives from the sponsor, host institution and the regulatory authorities for monitoring, audits and inspections. The study will comply with the Data Protection Act and General Data Protection Regulation (2018) which requires data to be anonymised as soon as it is practical to do so.

## 14.7 Other Ethical Considerations

N/A

# DATA HANDLING AND RECORD KEEPING

All data collected will be kept strictly confidential and in accordance with the Data Protection Act 1998 and GDPR. The research staff will ensure that the participants’ anonymity is maintained. On all study-specific documents, other than the signed consent form and enrolment log, the participant will be identified by initials and/or a participant ID number, not by name.

All research data will be kept in a secure location within UHL accessible only by named members of the research team during the active phase of the study and until the data have been analysed. It will then be archived in line with University of Leicester policy. Data will be stored for five years after the end of the trial and in line with University of Leicester archiving policy. The data will be carefully destroyed in accordance with University of Leicester policy after the retention period has elapsed.

Direct access to information gathered in this study will only be available to individuals who have been granted access. The sponsor, host institution and regulatory authorities can permit trial related monitoring, audits and inspections.

All study documentation containing identifiable participant data will be managed in accordance with ICH-GCP, Research Governance Framework for Health and Social Care and the Data Protection Act. Information will only be obtained from the participant if necessary for the study.

All electronic data will be stored on secure university (UOL) or hospital (UHL) network drives, to which only the relevant study staff have access, which is granted by the research team. All study documents and data will be kept for 5 years or the minimum determined by the regulatory authorities, whichever is longer. The study file will be archived in line with the Sponsor SOP.

Paper copies of the CRFs will be stored in a locked filing cabinet in the research office or lockable archive room in the LDC or in the academic building in Leicester General Hospital. Neither hard copies nor electronic files containing personal information will be removed from the research office or stored in a non-secure manner electronically. The study research team will comply with the Data Protection Policy of the relevant NHS Trust/Sponsor SOP.

# STUDY GOVERNANCE

## 16.1 Trial Steering Committee (TSC)

There will be no trial steering committee for this study. Regular meeting will be conducted with the study team, academic supervisors and the CI to discuss study progress.

## 16.2 Data Safety Monitoring Committee (DSMC)

There will be no data safety monitoring committee. All data safety matters will be reviewed on a regular basis by the study team, academic supervisors and the CI.

## 16.3 Trial Management Meetings

The investigators will meet regularly (approximately every two weeks) to discuss the progression of the trial and to highlight any important matters relevant to the continuation of the study.

# FINANCING AND INSURANCE

**Funder:** This research will be funded by Professor Kamlesh Khunti NIHR Senior Investigator Award, the NIHR Leicester Biomedical Research Centre, which is a partnership between University Hospitals of Leicester NHS Trust, Loughborough University and the University of Leicester.

Sponsorship and indemnity for the study will be provided by the University of Leicester. If a participant is harmed due to negligence this would be covered by the NHS Trust(s) indemnity arrangements for all participants in clinical trials. If a study participant wishes to make a complaint about any aspects of the way they have been treated or approached during the research project, the standard National Health Service complaint system will be available to them.

All costs are detaled bellow:

|  |  |
| --- | --- |
| Laboratory and Pathology analysis costs: | £5299.46 |
| Consumable costs: | £112.00 |
| Administrative costs: | £1,494.00 |
| Total study cost: | £6,905.46 |

For more information about the breakdown of the study costings see Excel spreadsheet named: RESPONSE Study\_Costing, v1.0\_25.06.2020.xlsx

# PUBLICATION POLICY

It is envisaged that the results of the study will be published in relevant medical or behavioural journals. Results may also be presented in educational presentations and conference presentations. Acknowledgement of any supporting organisations, including funders, the University Hospitals of Leicester, and the University of Leicester will be included.

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**Appendix 1. Alternative methods for conducting the RESPONSE study should participants be restricted from attending the research centre**

In the event of the study being restricted by social distancing measures, it will only involve remote contact with participants. The study will involve participants being walked through baseline data collection procedures via a video chat platform, a 4-week intervention to break up prolonged sitting time (with regular telephone/video chat to monitor progress and adherence), and finally participants being walked through the follow-up data collection via a video chat platform.

Should restrictions be introduced par way through the study, then all participants already recruited will be transferred to remote data collection and all future participants will only receive remote data collection. Should restrictions be lifted part way through the study, when the research team will make a decision based on how many participants have gone through remote data collection as to whether to continue with remote collection or to transfer to in-person data collection. Regardless of data collection method, the intervention will remain the same for all participants in the study,

**Objectives of Socially distanced intervention (should social distancing measures restrict attendance at research centre)**

Primary

* To investigate the effectiveness of an intervention designed to reduce prolonged sitting time administered remotely online and through telephone and video calls.

Secondary

* To investigate the effectiveness of the intervention for improving variability in blood glucose (weekly average) and time spent in hypo- and hyper-glycaemia.
* To investigate the effectiveness of an intervention for improving physical function.
* To investigate the effectiveness of the intervention for changing sedentary behaviour, sleep, and physical activity.

Additional Inclusion Criteria

* Stable internet connection, webcam, microphone, and speakers to allow for participation in video calls and uploading of information from physical activity trackers.

**4-week intervention for breaking up sitting time**

Recruitment from primary and secondary care, previous studies within which participants have agreed to be contact for future studies, and diabetes databases and registries.

***Week 0 – Screening (Telephone/Video chat)***

* Review of eligibility criteria
* Explanation of study procedures
* Read, sign, and return Informed Consent (pre-paid envelope)

***Week 7 – Remote Follow-up Assessments (Identical to Week 1)***

* Anthropometrics
* Questionnaires (WHO-DAS, Sarc-F, EQ-5D-5L, mMRC Dyspnoea, HADS, UKDDQ, NMQ, CFQ-11)
* Functional tests (MAT-sf, 30-SCST, 4-MGST)

***Week 1 – Baseline Assessments (remote capture)***

8-day monitoring with activPAL and CGMS. Wrist-worn activity monitor to be worn for study duration.

***Week 6 – Accelerometer monitoring and CGMS***

* Repeat free living measurements during final 8-days of intervention period

*Weekly 1-2-1 (telephone or video chat) review with research team*

CGMS: continuous glucose monitoring system; MAT-sf: Mobility Assessment Tool-sf; 30-CSTS: 30-seconds Chair Stand Test; 4-MGST: 4-meter Gait Speed Test

*Personalised recommendations based on sleep patterns, meal timings, and 24-hour blood glucose profile.*

**Figure 6. Trial Schematic (Alternative)**

**Table 5. Timeline of alternative study.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Phases (non-contact)** | **Weeks** | | | | | | |
| **1** | **2** | **3** | **4** | **5** | **6** | **7** |
| **Baseline Assessment** |  |  |  |  |  |  |  |
| **Free-living Assessment** |  |  |  |  |  |  |  |
| **Intervention** |  |  |  |  |  |  |  |
| **Free-living Assessment** |  |  |  |  |  |  |  |
| **Follow-up Assessment** |  |  |  |  |  |  |  |

**Consent**

Potential participants who show interest will be sent a copy of the PIS and informed consent documents. They will be given the opportunity to discuss any queries they have with a member of the study team over the phone/video chat. Should the participant wish to proceed, signed informed consent documents will then be returned to the study team in prepaid envelopes provided.

**Safety Considerations**

It will be recommended to participants that they create a safe space to conduct the assessments. The room should be free from clutter and large enough that they will be able to complete the assessments without any undue risk. If possible, participants should complete the assessments with someone else present in case of an unforeseen medical emergency. In the unlikely event that there is a medical emergency, and no one is present, the researcher will contact the emergency services.

**Baseline Assessments (alternative)**

Anthropometrics

Participants will complete a health questionnaire including their date of birth, sex, ethnicity, and medical history will be provided. Participants will be requested to measure their own waist circumference (midpoint between the lower costal margin and iliac crest). Tape measure will be provided and instructions on how to do this will be given.

Questionnaires

All questionnaires (as detailed in Section 8.3 – Baseline Assessments) will be provided to participants either in a digital format or in print format (delivered by post), to be completed and returned to the study team.

Physical Function

Physical function will be assessed remotely through the 30-second Chair Stand Test (30-SCST)82, the Mobility Assessment Tool-sf (MAT-sf)83, and the 4-meter gait speed test (4-MGST)84 (using a tape measure provided by the research team).

Physical Activity Monitoring and CGMS

Participants will be posted a wrist worn accelerometer, the activPAL device, and a CGMS. Participants will be asked to wear a wrist worn accelerometer device 24hours/day for the duration of the study on their non-dominant wrist.

The participants will be given instructions on how to apply the activPAL device and will wear the device on their thigh 24hours/day for up to 8-days before the start of the intervention and during the final 8-days of the intervention. The device will be initialised using the manufactures software under default settings. Waterproofing of the device will be achieved using a nitrile sleeve and Hypafix dressing. Alongside this, participants will fill out a wake and sleep log for the days they wear the devices and record any time when the devices are removed.

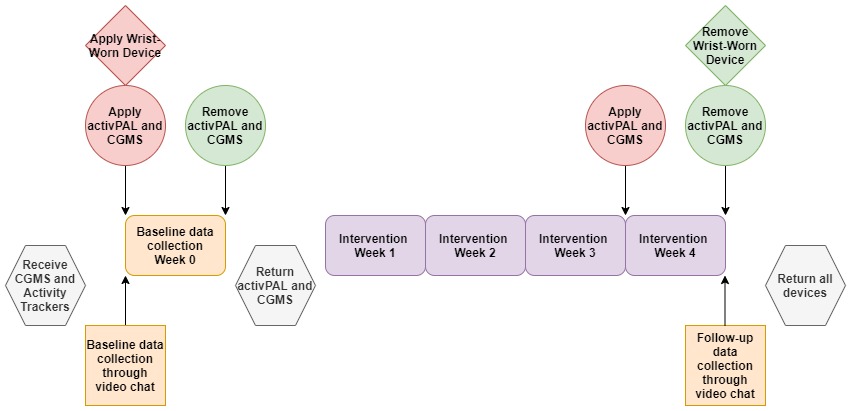
Participants will receive instructions on how to apply the CGMS. The CGMS will be worn on the participant’s back or stomach 24hours/day for up to 8-days before the start of the intervention and during the final 8-days of the intervention. As with the activity monitors, participants will receive instructions from the study team on proper placement of the device. The device will be returned along with the activity monitors in a prepaid envelope.

**Intervention**

The intervention will begin after the first 8-day activity monitoring has finished. The participants will receive guidance and advice from the study team on strategies to reduce their prolonged sitting time by 30-minutes per day. Participants will also receive regular calls/video calls from the study team to answer any questions and monitor adherence. During the final 8-days of the intervention, participants will wear activity trackers and CGMS as they did during baseline data collection.

**Follow-up**

Following the 4-week intervention, participants will complete follow-up assessments through video chat, which will replicate the baseline assessments.



**Figure 7. Schematic of alternative study structure**

**Table 4. Alternative Trial Procedures**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Measure** | **Method** | **Outcome** | **Measurements at each time point (contact)** | | |
| **Baseline** | **Follow-up** |
| Biochemical Analysis | CGMS | Blood Glucose | x | x |
| Accelerometers |  | Sedentary Behaviour | x | x |
| Physical Activity | x | x |
| Sleep Patterns | x | x |
| Questionnaires | WHO-DAS | Functional Capacity/Disability | x | x |
| Sarc-F | Functional Capacity/Disability | x | x |
| HADS | Anxiety/Depression | x | x |
| mMRC Dyspnoea Scale | Breathlessness | x | x |
| UKDDQ | Dietary Intake | x | x |
| EQ-5D-5L | Quality of Life | x | x |
| CFQ-11 | Fatigue | x | x |
| MEQ | Chronotype | x | x |
| NMQ | Chronic Pain | x | x |
| Anthropometrics |  |  |  |  |
|  |  |  |  |
|  | Waist Circumference | x | x |
| Physical Function | MAT-sf | Physical Function | x | x |
| 30-SCST | Physical Function | x | x |
| 4-MGST | Gait Speed | x | x |