Can High-Intensity Interval Training (HIIT) reduce the risk of diabetes relapse following discharge from the NHS Path to Remission Programme? – a pilot study

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Short title: HIIT post LCD

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SYNOPSIS

Title	Can High-Intensity Interval Training (HIIT) reduce the risk of diabetes relapse following discharge from the NHS Path to Remission Programme? – a pilot study
Short title	HIIT post LCD
Chief Investigator	Professor Iskandar Idris
Objectives	To determine the effect of a 16-week home-based HIIT intervention on markers of glucose metabolism and glycaemic control in individuals with T2D that have achieved diabetes remission in the NHS Path to Remission Programme.
Trial Configuration	Parallel group, non-blinded, randomised control study
Setting	Clinical research facility (Postgraduate Centre, University of Nottingham, Derby Campus)
Sample size estimate	This is a pilot study, therefore no power calculation has been performed
Number of participants	20 participants will be recruited and allocated 1:1 into intervention or control groups
Eligibility criteria	• Adults between the age of 18-70 years • Ability to provide informed consent. • Completed the NHS Path to Remission programme and achieved diabetes remission (HbA1c <48mmol/mol (6.5%), and off diabetes medications for at least three months)
Description of interventions	The intervention group will participate in a 16-week HIIT programme involving 3 sessions per week in their own homes. The HIIT sessions are comprised of five 1-minute intervals of body-weight exercises interspersed with 90-second active recovery periods. The control group will continue with their usual levels of activity.
Duration of study	Each participant will be involved in the study for 16 weeks. The study is expected to commence in November 2024 and be completed by the end of August 2026.
Randomisation and blinding	Participants will be randomised to the two groups using the "sealed envelope" online software. Research staff in direct contact with participants will not be blinded, however staff involved solely in analysis of samples and data will be blinded to the randomisation of participants.
Outcome measures	The primary endpoint for this study will be beta-cell function assessed during an intravenous glucose tolerance test (IVGTT) Secondary outcome measures include: • Insulin sensitivity • Overall glycaemic control • Body weight • Body composition • Skeletal muscle function

	• Skeletal muscle structure • Cardiorespiratory fitness (measured as VO_{2max} during cardiopulmonary exercise testing, CPET)
Statistical methods	Data will be statistically analysed using GraphPad Prism v10.1.2 (La Jolla, USA). Outcomes will be tested for significant within-group and between-group differences in pre-intervention and post-intervention means using two-way analysis of variance (ANOVA). Additionally, mean change in outcomes will be tested for statistical significance between the two groups using the independent samples t-test (or non-parametric alternative if data are not normally distributed).

ABBREVIATIONS

ABCD	Association of British Clinical Diabetologists
ACCP	American College of Chest Physicians
AE	Adverse Event
ANOVA	Analysis of variance
AT	Aerobic threshold
ATS	American Thoracic Society
BIA	Bioimpedance analysis
BMI	Body mass index
CI	Chief Investigator overall
COMAP	Centre Of Metabolism, Ageing & Physiology
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary exercise test
CRF	Case Report Form
CV	Curriculum vitae
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
EMG	Electromyography
GCP	Good Clinical Practice
HbA1c	Glycated haemoglobin
HIIT	High-intensity interval training
HRA	Health Research Authority
HR_{max}	Maximum heart rate
ICF	Informed Consent Form
IVGTT	Intravenous glucose tolerance test
LCD	Low calorie diet

NHS	National Health Service
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
PTR	Path to Remission
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event
SD	Standard deviation
T2D	Type 2 diabetes
VLCD	Very-low calorie diet
VO_{2max}	Maximum rate of oxygen consumption

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TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

Type 2 diabetes (T2D) currently affects nearly 3 million people in England and Wales and this number is continuing to rise (Diabetes UK, 2014; Gatineau *et al.*, 2014). By 2030, the number of adults with T2D is projected to rise to nearly 5 million, equating to approximately 10% of the adult population (Diabetes UK, 2014; Gatineau *et al.*, 2014). Treatment of T2D already uses a significant proportion of UK National Health Service (NHS) funding, currently costing approximately £9 billion (nearly 10% of overall spending) (Hex *et al.*, 2012). With the rising prevalence of T2D, this financial burden will only increase and could place a significant strain on an ever-constricted healthcare budget. As a consequence, interventions are required to manage T2D in a cost-effective manner that will help stem the progression of the condition, and halt the unrelenting rise in prevalence.

One particular intervention that has been growing in popularity recently is the very-low calorie diet (VLCD). In individuals with T2D, VLCD can induce significant weight loss (Leslie *et al.*, 2017; Churuangsuk *et al.*, 2022), improvements in glycaemic control (Sellahewa *et al.*, 2017; Kloecker *et al.*, 2019), and in particular cases can result in T2D remission (Steven *et al.*, 2016; Bynoe *et al.*, 2019). The remission of diabetes has been shown to be strongly associated with significant improvements in insulin sensitivity, and pancreatic beta cell function, particularly the first phase response of insulin secretion (Lim *et al.*, 2011; Taylor, 2013; Steven *et al.*, 2016). Following this, several large-scale population studies have demonstrated the efficacy of interventions based on VLCD principles in the clinical setting (Astbury *et al.*, 2018; Lean *et al.*, 2018; Taheri *et al.*, 2020). This has led to the development of the NHS Path to Remission programme, in which individuals with T2D are referred for an intensive dietary intervention for a year (Diabetes UK, 2018; NHS England, 2020). The aim of this programme is to use an intervention based on VLCD principles to induce diabetes remission for the first 3-5 months, with the remaining time used to embed behaviours that result in long term maintenance of the remission.

Unfortunately, one of the drawbacks of intensive caloric restriction interventions such as VLCD is the risk of weight regain and diabetes relapse (Saris, 2001; Lean and Hankey, 2018). Accordingly, long-term follow-up from the precursor of the NHS Path to Remission Programme suggests that by 2 year a significant proportion of participants had experienced T2D relapse (Lean *et al.*, 2019), and by 5 years, this figure had risen to greater than 80% (Lean *et al.*, 2024). Not only is this disappointing for the patients involved, it causes significant cost to the NHS, which spends between £2000 - £3500 per year on managing individuals with T2D (Wang *et al.*, 2022; Diabetes.co.uk: the global diabetes community, 2023). Thus, there is compelling benefit to identifying methods to reduce this risk of diabetes relapse to patients, as well as the wider healthcare system.

High-intensity interval training (HIIT) has received growing interest as an option for the treatment of many health conditions. HIIT has been demonstrated to confer significantly greater improvements in aerobic fitness (measured as VO_{2max}) compared to other forms of exercise in healthy individuals (Milanović, Sporiš and Weston, 2015), patients with ischaemic heart disease (Liou *et al.*, 2016; Hannan *et al.*, 2018), heart failure (Weston, Wisløff and Coombes, 2014), obesity (Türk *et al.*, 2017) and T2D (De Nardi *et al.*, 2018). It has also been shown in multiple meta-analyses to be safe, even in patients with significant cardiac disease (Weston, Wisløff and Coombes, 2014; Cassidy *et al.*, 2017; Hannan *et al.*, 2018).

Also relevant to people with T2D are the positive effects of HIIT on multiple measures of glycaemic control with studies reporting reduced fasting glucose (Fex *et al.*, 2015; Winding *et al.*, 2018) and improved overall HbA1c (Cassidy *et al.*, 2017). HIIT in this patient group also improves cardiac function (Cassidy *et al.*, 2016), blood pressure (De Nardi *et al.*, 2018),

macrovascular and microvascular function (Mitranun *et al.*, 2014) and liver fat (Cassidy *et al.*, 2016). Most pertinently, HIIT has also been associated with improved insulin sensitivity (Jelleyman *et al.*, 2015; Gillen *et al.*, 2016), enhanced pancreatic β cell function (Madsen *et al.*, 2015a).

One of the most attractive features of HIIT is its time-efficiency with most protocols requiring a commitment of 45 – 60 minutes per week. Despite this being less than half the amount of time recommended by international guidelines (World Health Organisation, 2010), outcomes from HIIT interventions are equivalent, or often superior, to those observed with other forms of aerobic exercise (Gillen *et al.*, 2016; De Nardi *et al.*, 2018; Winding *et al.*, 2018). Moreover, HIIT can be performed at home, without the requirement of expensive exercise equipment or direct supervision. Thus, HIIT can overcome several of the widely cited barriers to engagement with exercise, including lack of time, the high cost of exercise facilities, dislike of gym-based programmes and fear of exercising in public.

In the University of Nottingham Centre Of Metabolism, Ageing & Physiology (COMAP) department, we have developed a novel home-based body-weight HIIT programme. This programme has been previously studied in a group of 18 middle-aged participants for 4 weeks, in comparison to a supervised laboratory HIIT programme and demonstrated similar results between the two groups (Blackwell *et al.*, 2017). This suggests that our home-based programme is *as effective* at improving cardiovascular fitness as a laboratory-based protocol.

As previously outlined, HIIT has demonstrated positive effects pancreatic beta cell function, and insulin resistance, and deterioration in these parameters, particularly beta cell function is associated with diabetes relapse. We therefore hypothesise that engaging in a HIIT intervention after achieving diabetes remission and being discharged from the Path to Remission programme will prevent the deterioration in beta cell function and insulin resistance. This would suggest that HIIT could improve maintenance of long-term diabetes remission. Thus, we are conducting this pilot study which will be the first of its kind to be performed. The results from this study will form an initial evidence-base regarding use of this intervention in this setting and will be used to inform the possible development of larger studies aimed at determining the real-world application of home-based HIIT programmes for maintenance of diabetes remission.

TRIAL / STUDY OBJECTIVES AND PURPOSE

PURPOSE

The purpose of this study is to determine the effect of a 16-week home-based HIIT intervention on markers of glucose metabolism and glycaemic control in individuals with T2D that have achieved diabetes remission in the NHS Path to Remission Programme. This will be compared against a control group who will not be involved in any exercise intervention (thus will receive usual care).

PRIMARY OBJECTIVE

Objective: To investigate whether a 16-week home-based HIIT intervention will improve beta-cell function in a group of individuals with T2D that have achieved diabetes remission, compared to a control group participating in no exercise intervention
Hypothesis: Participation in the HIIT intervention will elicit significant improvements in beta-cell function compared to not participating in any exercise intervention

SECONDARY OBJECTIVES

Objective: To determine whether this home-based HIIT intervention will also lead to greater improvements in glycaemic control and insulin sensitivity in these individuals, compared to no exercise intervention

Hypothesis: Participation in the home-based HIIT intervention will result in significantly improved glycaemic control and insulin sensitivity, compared to not participating in any exercise intervention

Objective: To establish the effects of this home-based HIIT intervention, compared to no exercise, on body weight, body composition and cardiorespiratory fitness (VO_{2max}) in these individuals

Hypothesis: Participation in the home-based HIIT intervention will significantly reduce body weight & body fat, whilst also increasing lean mass & VO_{2max} compared to not participating in any exercise intervention

DETAILS OF PRODUCT(S)

This study will not be investigating the physiological effects of any medicinal products. However, one product will be used to assist in measuring some of the outcomes and is described below.

Description

20% glucose solution – this is a solution of dextrose sugar that contains 20g per every 100ml of fluid. This will be administered intravenously to participants during the IVGTT to stimulate an insulin response. This is widely utilised in clinical studies for the calculation of pancreatic beta cell function and insulin sensitivity, as well as in clinical practice to provide care to patients.

Manufacture

20% glucose – Baxter International, USA

Packaging and labelling

The glucose solution is packaged and labelled by the manufacturers prior to purchase and delivery to the research facility.

Storage, dispensing and return

The glucose solution will be stored in a cool, dry area at room temperature, in accordance with the manufacturer's instructions. This area is located within a restricted access section of the research department when only researchers can access. Any solution remaining following use on a study day will be discarded.

Placebo

There will be no placebo for this study.

Known Side Effects

The incidence of side effects to intravenous glucose is very rare. Side effects identified in literature include chills, fever, electrolyte and fluid imbalance, hypersensitivity, localised reaction or pain, rash or venous thrombosis. However, these are very rarely encountered despite glucose being frequently used in clinical practice and clinical studies.

Reference source:

British National Formulary https://bnf.nice.org.uk/drug/glucose.html

TRIAL / STUDY DESIGN

TRIAL / STUDY CONFIGURATION

This study will be a single-centre, randomised, non-blinded physiological study.

Primary endpoint

The primary endpoint for this study will be pancreatic beta cell function, determined as the incremental suprabasal insulin concentration during the first 10 minutes of an intravenous glucose tolerance test (IVGTT)

Secondary endpoints

1. Insulin sensitivity – measured during the intravenous glucose tolerance test (IVGTT) and calculated from fasting glucose and insulin using the homeostatic model of assessment for insulin resistance
2. Overall glycaemic control – assessed from measurement of glycated haemoglobin (HbA1c)
3. Body weight
4. Body composition – deduced from bioimpedance analysis (BIA)
5. Skeletal muscle function – assessed using muscle strength testing and electromyography
6. Skeletal muscle structure – using muscle ultrasonography
7. Cardiorespiratory fitness – determined from be the highest rate of oxygen consumption obtained (VO_{2max}) during a cardiopulmonary exercise test (CPET)

Safety endpoints

HIIT is well known to be a safe intervention in individuals with T2D. Therefore, as such, there are no safety endpoints in this study.

However, the safety of participants in the study will be rigorously maintained. Participants will be monitored during the study days for any adverse events associated with any of the procedures performed. In particular, participants will be monitored extensively during the CPET with continuous heart rate, blood pressure, pulse oximetry and electrocardiogram (ECG) monitoring throughout. Each CPET session will be supervised by members of the research team, one of which is a medically trained clinician who will be present throughout the session. In the unlikely event of a participant requiring urgent medical attention, initial first aid will be provided and emergency services contacted if required. Our department has conducted multiple studies in which CPETs are performed and has no incidences of adverse events during these assessments.

The intervention of this study will require participants to perform body-weight HIIT in their own home environment. Each participant's safety and suitability for engagement in such exercise will be assessed rigorously during the initial screening and baseline exercise testing. If any concerns become apparent at this stage then the participant will be removed from the study on the basis of their safety. Whilst exercising at home, participants will be provided with a list of concerning symptoms to be aware of, and advised to contact emergency services immediately if these symptoms were to develop. In addition, we will suggest to participants that they have another person in the near vicinity when performing their HIIT sessions – particularly for the initial sessions.

Stopping rules and discontinuation

The safety of participants is of utmost importance to our study group. Participants' continuation in the study would be deemed unsuitable if they were to develop any persistent, uncomfortable or clinically significant symptoms in response to any elements of the intervention(s) or procedures. Alongside the participants' right to withdraw from the study whenever they choose, the study team reserves the right to discontinue a participant's involvement if the Chief Investigator decides that continued involvement is not in their best interests. The basis of this decision will be discussed with the participant to achieve a mutually agreed outcome.

There are some criteria that would warrant immediate removal from the study, to ensure the safety of the participants in relation to the exercise element of this study. In particular, immediately removal will be considered if a participant were to develop any of the following symptoms during any exercise sessions (CPET or HIIT):

- Chest pain or tightness,
- Palpitations,
- Faintness,
- Sudden pallor,
- Loss of co-ordination,
- Confusion,
- Dizziness, or
- Excessive breathlessness

Participants will be given lay language information detailing these symptoms to ensure that they are aware of them at all times, especially when performing the HIIT sessions in their home environment.

In addition, as participants will be monitored during their CPET sessions, they will also be observed for the following signs:

- Changes on continuous ECG monitoring suggestive of ischaemia (e.g. >2mm ST depression) or arrhythmia
- Systolic blood pressure rising >250mmHg
- Diastolic blood pressure rising >120mmHg
- Blood pressure drop of >20mmHg
- Drop in heart rate >10 beats per minute
- Oxygen saturations <94%

If any of these were to occur during the CPET session then this will also be grounds for removal from the study to ensure the safety of the participants.

Participants will also be encouraged to report any injuries that occur during the exercise sessions. With all injuries, a discussion will be held to determine whether removal is appropriate, however, in the case of any injuries that requires medical intervention, an individual's participation will be discontinued.

RANDOMIZATION AND BLINDING

Participants will be recruited to the study by the Co-Investigator Dr Oluwaseun Anyiam and the Chief Investigator Professor Iskandar Idris. All participants will go through an initial screening appointment and then a final decision regarding recruitment will be made after discussion between the study investigators. Following this, they will be randomised to either the intervention or control groups by Dr Oluwaseun Anyiam using the online "Sealed Envelope" software (www.sealedenvelope.com), which is the standard method of randomisation utilised for studies in this research department. The randomisation ratio will be 1:1 and the allocation

sequence will be generated by an algorithm within the online software, and as such, will be third party.

This study will be investigating the effects of an exercise intervention. Due to the nature of this intervention and the processes required to safely monitor the intervention group, blinding of participants or study investigators will not be possible. However, any research staff involved solely in data analysis will be blinded to the group that participants are allocated to. Neither those involved in data analysis, nor the study statistician will have contact with participants.

Maintenance of randomisation codes and procedures for breaking code

Blinding of participants and research staff is not possible in this study, therefore will not be used. Thus, there will not be any randomisation codes and no need to break a randomisation code. In the event of an SAE, the group in which the participant has been allocated to will be easily accessible from the study master file, which can be accessed by the Chief Investigator or any of the Co-Investigators.

TRIAL/STUDY MANAGEMENT

The trial will be managed by a single assigned project manager. There will not be a Trial Steering Committee, Management Group or Data Monitoring Committee for this.

The Chief Investigator has overall responsibility for the study and shall oversee all study management. The data custodian will be the Chief Investigator. The Chief Investigator will also oversee the training of study investigators to ensure that they have the necessary competences to perform the procedures required for this study.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

Study Duration:
The study is expected to be run for 21 months, and recruitment will begin once ethical approval has been obtained. The current expectation is to begin recruitment by November 2024 and the final study visit to occur by the end of August 2026.

Participant Duration:
The participants will be involved in the study for 16 weeks. There is no run-in period required for the study, and participants on regular medications will be advised to continue them as usual. There will be no specific follow-up after the final visit.

End of the Trial

The end of the study will be the last study visit of the last participant.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

The study will be conducted in the Centre Of Metabolism, Ageing & Physiology (COMAP) department in the University of Nottingham's Royal Derby Hospital campus. This is a research facility based in a university building that is based on the same site and linked to a secondary care hospital. Moreover, this research department inhabits several hospital clinicians working within it and facilitates numerous studies pertaining to musculoskeletal physiology. In the last 5 years, three studies involving HIIT have been successfully recruited to and completed.

Participants will be identified directly from Xyla Health who are the local providers of the Path to Remission programme. The programme runs on a regional basis and we intend to recruit from our local region, Derbyshire. Both the Chief Investigator and Dr Oluwaseun Anyiam have strong links with the coordinators of the programme in this region. Staff members of the local Path to Remission programme provider will be made aware of the study. They will send an email to the patients that have consented to receiving marketing communication from Xyla Health, informing them about the study. This email will contain the email address of a member of the study team advising any interested patients to get in contact. If patients make contact with the research team, expressing an interest in the study, they will be forwarded a study PIS to read by the research team. The Path to Remission programme staff will not be involved in any aspect of eligibility screening for potential participants.

Once prospective participants have been sent a PIS, a member of the research team will contact them (by phone or online meeting) to discuss all aspects pertaining to participation in the study and go through some initial screening questions. Following this, a formal screening appointment will be arranged where the study procedures will be explained again and consent to participate will be sought. Individuals who lack the capacity to make decisions or provide informed consent will not be included in this study. Individuals whose primary language is not English, and whose ability to communicate in English prevents the acquisition of adequate informed consent, will also not be recruited, as a safety precaution due to the need for effective and frequent communication during the intervention period.

It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

Eligibility criteria

Inclusion criteria

- Adults between the age of 18-70 years
- Ability to provide informed consent.
- Completed the NHS Path to Remission programme and achieved diabetes remission (HbA1c <48mmol/mol (6.5%), and off diabetes medications for at least three months)

Exclusion criteria

- BMI > 40kg·m^2
- Current participation in a formal exercise regime
- Current pregnancy or breastfeeding
- Uncontrolled hypertension (blood pressure >160/100mmHg)
- History of cardiovascular disease:
  - Symptomatic angina
  - Heart failure (class III/IV)
  - Significant arrhythmias
  - Right to left cardiac shunt
  - Recent acute coronary syndrome
  - Severe aortic valvular disease
  - Active cardiac infection
- Background of the following respiratory diseases:

  - Pulmonary hypertension
  - Significant COPD
  - Uncontrolled asthma
- History of malignancy undergoing current treatment or palliation
- Presence of significant musculoskeletal, neurological or cerebrovascular disease
- Any other medical condition deemed by the investigators to preclude inclusion into the study

These exclusion criteria are based on the contraindications listed in the American Thoracic Society / American College of Chest Physicians statement on CPET (ATS/ACCP, 2003).

Expected duration of participant participation

Study participants will be participating in the study for 16 weeks.

Removal of participants from therapy or assessments/Participant Withdrawal

Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

Participants may be removed temporarily or permanently depending on the prevailing circumstances around the time of the decision. Grounds for temporary removal from the study include (but are not limited to):

- very mild joint or limb injury (not requiring medical attention)
- inability to continue with the exercise intervention due to unforeseen personal circumstances (e.g. bereavement)

Participants will be permanently removed from the study in the following situations:

- withdrawal of consent
- significant injury (requiring medical attention)
- development of any high-risk symptoms (listed above in the Exclusion Criteria section) whilst performing any of the home-based exercise sessions
- evidence of high-risk signs (listed above) during the CPET sessions
- failure to achieve minimum compliance with the exercise intervention

If a participant withdraws their consent after screening but before the first study visit, they may be replaced. Should a participant withdraw during or following the first study-visit, they will not be replaced, and instead, will be deemed to have dropped out of the study. As randomisation will occur immediately before the participant's first study visit, anyone who withdraws after randomisation will also be classed as a drop-out from the study.

For participants that are removed from the study, details of this decision will be documented in the CRF. The date and time of removal will be documented, as well as the reason for doing so (if provided). A decision to remove any participant that is made by the research team, will be discussed with the Chief Investigator and will require final agreement by them. We do not envisage any potential issues with abrupt withdrawal from the study and therefore, do not have measures to prevent any issues. Participants that are withdrawn will be advised to continue their care arrangements with their General Practitioner, and a letter will be sent to the General Practitioner informing them of the individual's participation in the study – in the same way as for all participants who complete the study.

Informed consent

All participants will provide written informed consent. The Informed Consent Form will be signed and dated by the participant before they enter the trial. The Investigator will explain the details of the trial and provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation.

Informed consent will be collected from each participant before they undergo any interventions (including physical examination and history taking) related to the study. One copy of this will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the patient's hospital records.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant.

Consent will be obtained during an initial screening visit, prior to proceeding with the medical assessment. In advance of the screening visit, the PIS will be sent to prospective participants for them to familiarise themselves with the study details. The PIS will then be discussed in full with the prospective participant during this visit. There will be specific reference to the exercise intervention and the study visits. They will then be given sufficient time to ask any questions they may have related to the study protocol. Following this, their consent will be sought, ensuring that they have enough understanding of the study beforehand.

At each study visit, verbal consent to continue with the study will be obtained and documented in the trial master file. In addition, participants will be contacted (by phone or e-mail) regularly during the 16-week intervention period and again, their verbal consent to continue will be sought at every opportunity.

TRIAL / STUDY TREATMENT AND REGIMEN

All study visits and laboratory analysis will take place on university premises in the clinical research facility based in the Royal Derby Hospital site of the University of Nottingham. The study will last a total of 16 weeks and will involve three visits to the research facility for each participant. The structure of the study is outlined in Figure 1.

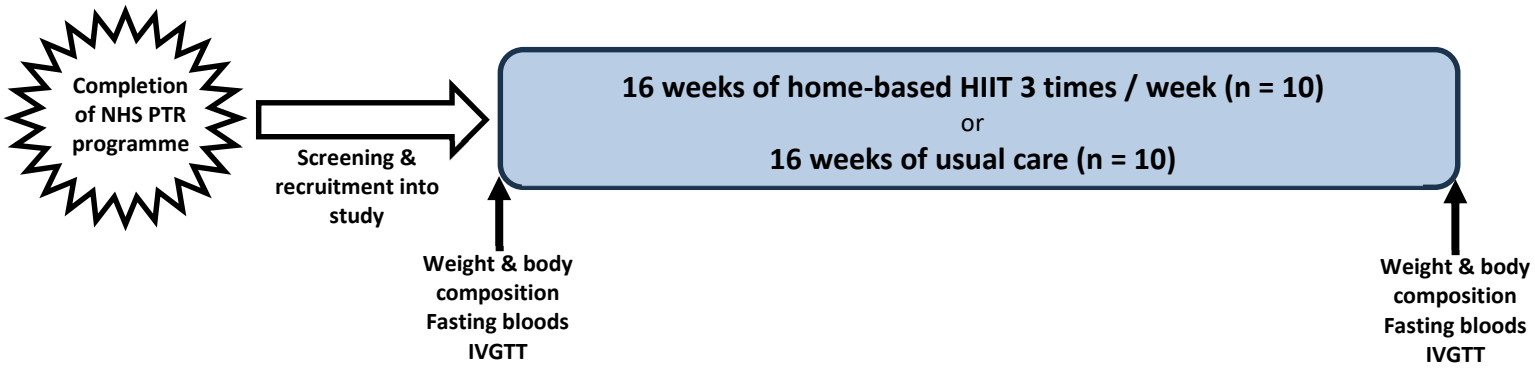


Figure 1: Schematic representation of the study protocol

Screening

Prior to entry into the study, prospective participants will be contacted to discuss the study details in full and go through some initial screening questions, as described previously. They

will then be invited for a screening appointment, during which informed consent will be sought, and a full medical screening will be performed by a study clinician to assess an individual's suitability for recruitment into the study. This will involve a full medical history, assessment of height & weight, ECG and venepuncture to check HbA1c, lipid profile, full blood count, urea & electrolytes, liver function tests and thyroid function tests. Before leaving, prospective participants will be offered an orientation tour of the research department and have a light session on the exercise testing bicycle to familiarise them to the equipment prior to the CPET test on the first study day.

A paper copy of the blood test results will be sent to the department. These, along with the rest of the screening information will be reviewed by a clinical member of the research team and discussed with the Chief Investigator, who will make the final decision regarding recruitment. Any abnormal results will be discussed with the prospective participant and their General Practitioner will be informed to ensure this is followed-up appropriately. If an individual is deemed to be suitable for recruitment into the study, they will be invited to attend their first study visit and a letter will be sent to their General Practitioner informing them of their involvement. Prior to the first study visit, the confirmed participant will be randomised into one of the following groups:

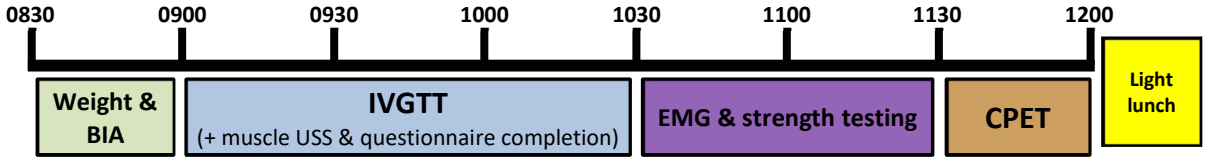
1. Intervention group
2. Control group

First study visit

The procedure for the first study visit will be identical for all participants, regardless of the group they have been randomised to. Participants will be asked to arrive at the clinical research facility between 0830 to 0900, after fasting from midnight the night before (water will be allowed). Upon arrival, they will have their body weight measured and BIA performed to provide an accurate measure of body composition.

Following this, the participant will be laid on a clinical examination bed in the reclined position in preparation for the IVGTT. Initially, an intravenous cannula will be inserted into the participants arm (by a trained clinical practitioner from within the research team) and fasting blood tests will be obtained. Another blood test for glucose and insulin will be obtained from the cannula 5-10 minutes later, and immediately after this, an intravenous bolus of 20% glucose will be administered, signifying the start of the IVGTT. The dose of 20% glucose administered will be calculated as 0.5g/kg body weight (up to a maximum of 35g i.e. 175ml of 20% glucose), as per standard IVGTT protocol (Bingley *et al.*, 1992). This calculation will be performed by the Co-Investigator Dr Oluwaseun Anyiam, who is experienced in calculations of infusion doses. Blood samples for glucose and insulin will be obtained at 2, 4, 6, 8, 10, 20, 30, 40, 50 & 60 minutes after the initial glucose bolus. The IVGTT is a well-established method for measuring insulin sensitivity and pancreatic beta cell function (Cersosimo *et al.*, 2014; Hannon *et al.*, 2018) and has been widely utilised in studies investigating a range of exercise interventions (Slentz *et al.*, 2009; Gillen *et al.*, 2016; Mora-Rodriguez *et al.*, 2019). A total of 50ml of blood will be drawn from the participants during the IVGTT. During the IVGTT, an ultrasound of the right vastus lateralis will be performed to assess muscle cross sectional area, fascicle length and pennation angle. Additionally, participants will be asked to complete questionnaires gathering information regarding their current physical activity and quality of life.

Upon completion of the IVGTT, participants will be escorted to a different laboratory containing bespoke equipment for muscle function assessment. Initially electromyography (EMG) of the right leg muscles will be performed at various contraction intensities. Next, they will undergo 1 repetition maximum strength testing of left knee extension. Finally, they will undergo a supervised CPET session to determine their VO_{2max} and aerobic threshold (AT). This will be performed on a cycle ergometer with continuous cardiopulmonary monitoring, as is standard practice within our research group (Boereboom *et al.*, 2016; Blackwell *et al.*, 2017). The CPET usually lasts between 8-15 minutes and is followed by a period of monitored recovery for up to 5 minutes. Before leaving, participants will be provided with a light lunch. It is expected that this study visit will last approximately 4 hours so should be completed before 1230. The schematic below provides a visual representation of the study visit.



Intervention Period

Following the first study day, participants randomised into the intervention group will enter the intervention period. These participants will be instructed to perform a HIIT protocol at home 3 times a week for 16 weeks. There will be some flexibility over the distribution of exercise sessions each week but they will be asked not to complete the 3 sessions on consecutive days.

Each session will begin with 2 minutes of jogging on-the-spot as a warm-up. Then participants will perform 5 intervals of exercises at a high intensity for 60 seconds. Each interval will be interspersed with 90 seconds of "active" recovery, involving walking on the spot. The 5 intervals will consist of the following exercises in this order:

1. Star jumps
2. Standing squats
3. On-the-spot sprints
4. Standing squats
5. Star jumps

This pyramid design has been chosen as it can be used to provide participants with a target of repetitions to achieve in the 4th and 5th interval (using the number of repetitions achieved in the 1st and 2nd).

After the fifth interval exercise, the session will end with another 2 minutes of light on-the-spot jogging. The entire HIIT protocol will last 15 minutes in total. Participants will be provided with a pulse oximeter to take home with them for monitoring of their heart rate and instructed to aim to achieve >85% of their maximum heart rate (HR_{max} – determined from the CPET on the first study day) during each session to ensure they are achieving the desired intensity. They will also receive an exercise documentation pack, in which they will be instructed to document the date and time of every exercise session, the maximum heart rate achieved during the session and any potential problems encountered.

To maintain the safety of participants during the intervention period, a number of measures will be put in place. It will be stressed to participants that if they were to develop any concerning symptoms during the HIIT sessions, they must seek immediate medical attention, either from emergency services, or their General Practitioner. We will ask participants to maintain particular awareness of the following symptoms:

- Chest pain or tightness,
- Palpitations,

- Faintness,
- Sudden pallor,
- Loss of co-ordination,
- Confusion,
- Dizziness, or
- Excessive breathlessness

These symptoms will be detailed in the exercise documentation pack so participants can refer to them during the exercise session. It will also be suggested to participants that they have another person in the near vicinity when performing the sessions (particularly the initial sessions), to ensure someone is immediately present to help obtain medical attention if required.

In addition, participants will be contacted regularly by phone, text or email throughout the intervention period by a member of the research team to discuss any problems, ensure their safety, assess compliance with the programme and obtain consent to continue. Participants in the intervention group will be contacted at least weekly for the first 4 weeks, then at least every two weeks thereafter. The control group will be contacted every two weeks. Participants will also be given a study-dedicated mobile phone number, on which they can contact a member of the research team if they have any queries or concerns that are directly related to their participation in the study.

The control group will not be participating in any exercise intervention. Participants in this group will be instructed to make no significant changes to their current levels of physical activity for the 16-week period.

All participants will be advised to continue their regular medications as prescribed. These regular medications will have been recorded at the screening appointment and documented in the CRF.

Final Visit

At the end of the 16 weeks (approximately 72 hours after their final HIIT session), all participants will undergo their final study visit. This will follow the exact same format of the first study visit, except at the end of this study visit participants will be asked to complete a feedback questionnaire, thanked for their involvement and exited from the study. Subsequently, their General Practitioner will be sent a letter detailing their results with a copy also sent directly to them. If participants have any questions regarding their results and ongoing management, they will be advised to discuss these with their General Practitioner.

Compliance

Participants in the intervention group will be asked to complete an exercise documentation pack, in which they will be required to record details of each exercise session performed. They will be contacted by phone (or email) at regular intervals (at least weekly) and compliance will be one of the issues discussed, with reference to their documentation pack.

Participants will be expected to perform the HIIT sessions 3 times per week. However, this can be increased to 4 times if a session has been missed from the previous week. Compliance will be deemed acceptable if >80% of sessions are performed. Participants will be excluded if they:

- are unable to complete 4 or more consecutive sessions
- miss more than 7 sessions in total
- fail to complete the set exercise regime in 7 or more sessions

The number of participants excluded due to poor compliance will be recorded and reported in the study report and any potential publications.

Criteria for terminating trial

The study is performed at a single centre so termination at this centre will result in termination of the whole study. Termination will be considered if it becomes clear that the intervention is resulting in an unacceptably high incidence of adverse events, such as acute cardiovascular events. However, this is of minimal likelihood as HIIT has been repeatedly demonstrated to be safe in patients with established cardiovascular disease, heart failure and T2D (Weston, Wisløff and Coombes, 2014; Cassidy *et al.*, 2017; Hannan *et al.*, 2018). Termination will also be considered if during the course of the study it becomes apparent that the majority of participants are not achieving full compliance (as described above). Responsibility for the decision to terminate the study will fall upon the Chief Investigator.

Participants in possession of any study equipment (i.e. pulse oximeters) will be requested to return these items as soon as is feasibly possible.

TRANSPORT AND STORAGE OF THE TISSUES

This study will require collection of blood samples in order to meet the study outcomes. The majority of samples will be analysed “in-house” within the Division of Medicinal Sciences and Graduate Entry Medicine, at the Royal Derby Hospital campus of the University of Nottingham. One blood sample from each analysis will require transfer to the pathology laboratory in the Royal Derby Hospital for HbA1c. These will be hand-delivered to the pathology laboratory (which is on the same site) and analysed immediately so do not require any storage. This study does not involve any collaborators, so there are no arrangements for transfer of samples to other sites.

Samples that are for analysis at a later date will a be stored within our department in -80°C freezers, in line with Human Tissues Act 2004 guidelines until analysis can be performed. Blood samples will be centrifuged initially, allowing removal of the cellular fraction, and the remaining plasma will be stored in aliquots. All -80°C freezers are monitored by the "Notion Pro" alarm system, which is directly integrated within the University of Nottingham alarm system. In the event of freezer failure, senior laboratory staff in the department are notified by email and text. If this situation were to occur, there is a well-established procedure for relocation of samples to back-up freezers within the department.

Samples will be stored in a linked anonymised format. Each sample will be labelled with a study reference number and unique participant code and cross referenced with location code numbers to ensure accurate linkage to study data and the consent form. There will not be any identifiable data on the samples. Participants’ data and their corresponding identification code will be kept in a secure cabinet/drawer, and in a master database which will be held by Dr Oluwaseun Anyiam in a password encrypted file. These data will only be accessible to the study investigators – thus it will not be readily accessible. Samples will only be identifiable by cross referencing the identification code with the securely stored personal data. Samples for NHS pathology analysis will be labelled in accordance with local NHS procedures.

Participants will be asked to provide additional consent if storage of samples for use in future research studies is required. If consent it obtained, samples will be stored at the research tissue bank in the Division of Medical Sciences and Graduate Entry Medicine, Royal Derby Hospital campus of the University of Nottingham (DI Dr James Dixon, Licence number 12265), as described above. If participants do not provide consent for the storage of their samples beyond completion of this study, their samples will accordingly be disposed of, as per the Human Tissues Act 2004, once analysis of the samples has fully concluded.

LABORATORY ANALYSES

Analysis of insulin concentrations will be undertaken in the Centre Of Metabolism, Ageing & Physiology (COMAP) department laboratories based in the Division of Medicinal Sciences and Graduate Entry Medicine, at the Royal Derby Hospital campus of the University of Nottingham. All of the laboratory procedures are well-established within the department. Sample analysis will be undertaken by trained staff (doctoral & postdoctoral research students and research technicians) who have received full training and attained standardised competency in the analytical methods. All methods have a formalised standard operating procedure which is regularly reviewed and updated as appropriate.

In addition, each piece of laboratory equipment within our department is maintained regularly in line with manufacturer recommendations, with routine maintenance and servicing being performed by trained laboratory staff. In the event of instrument failure, highly-trained staff are readily available to remedy the issues. If this is not possible, back-up procedures exist to ensure analysis can continue. In addition, there is access to instrument vendors and service engineers, who can be contacted promptly to provide replacement parts or new equipment altogether.

Blood is the only tissue that will be required to achieve the outcomes of this study. Blood samples will be collected during the IVGTT to measure serum glucose and insulin concentrations. Each blood sample will be split into multiple aliquots immediately upon obtaining it from the cannula. One aliquot (approx. 1ml) will be analysed in real-time with a YSI 2500 Biochemistry Analyser machine (YSI, Ohio) present in the department's clinical research rooms. The second aliquot (approx. 3ml) will be centrifuged, with the resulting supernatant collected into another tube. This supernatant will then be analysed using an enzyme-linked immunosorbent assay (ELISA) technique to determine serum insulin concentration.

Some blood samples (HbA1c, full blood count, urea & electrolytes, liver function tests, lipid profile and thyroid function tests) will be analysed in the NHS pathology laboratory within the Royal Derby Hospital using established protocols within their department. Each of these tests will be assessed in each prospective participant at the screening stage, and then HbA1c will be checked in each recruited participant at the first and final study visits.

STATISTICS

Methods

Data will be analysed within our research department based in the Division of Medicinal Sciences and Graduate Entry Medicine, at the Royal Derby Hospital campus of the University of Nottingham. Analysis will be performed primarily by Dr. Anyiam, under the supervision of Chief Investigator and other Co-Investigators. In addition, there will be oversight provided by the university support statistician. It will not be possible to blind the study investigators to the randomisation of participants. However, staff involved solely in analysis of samples and data will be blinded to the randomisation of participants. All analysed data will be stored and backed-up within a secure online data management system on the University of Nottingham's internal server.

Data will be analysed using the statistical programmes GraphPad Prism v10.2.1 (La Jolla, California, the USA), which is available on the university internal server. Prior to statistical analysis, data will be tested for normality using the Kolmogorov-Smirnov test. Normally distributed data will be expressed as mean (SD), whilst non-normally distributed data will be reported as median ± inter-quartile range.

The primary endpoint beta-cell function will be derived from the area-under-curve (AUC) of serum insulin concentration during the first 10 minutes of the IVGTT (Cersosimo *et al.*, 2014). This correlates well with the gold standard hyperinsulinaemic clamp (Rakotoambinina *et al.*, 1997) and can sensitively detect changes in beta cell function in response to dietary interventions (Jackness *et al.*, 2013; Liu *et al.*, 2015). Insulin sensitivity will be derived from serum glucose and insulin concentrations obtained during the IVGTT. An insulin sensitivity index developed by Tura *et al.* (Tura *et al.*, 2010) will be calculated, as well as HOMA2-IR from fasting glucose and insulin concentrations. Body composition measures (lean body mass and fat mass) will be directly determined from BIA.

Two-way analysis of variance (ANOVA) will be used to determine statistically significant differences between the mean baseline and follow-up measurements of all outcomes in both groups. Additionally, the independent samples t-test will be used to compare mean changes in outcomes between the two groups and test for statistical significant differences between them. Non-parametric alternatives will be used if data are non-normally distributed. If, despite randomisation, the mean value of an outcome at baseline is different between the groups then linear regression analysis will be performed to account for the baseline difference. The significance level will be set at p=0.05.

Interim analysis of available data will be performed 8-10 months into the course of the study, in order to inform the funding organisation that progress is being made. Finally, in order to maintain the safety of participants, the occurrence of adverse events will be continuously monitored and if an unacceptably high incidence of such events is noted, this will be highlighted to the Chief Investigator and Co-Investigators. At this point, a decision will be made regarding continuation of the study, or if other safety procedures are required to reduce the AE occurrence rate.

Sample size and justification

This is a pilot study, as such, no power calculation has been performed to justify sample size. However, a previous study with similar participant numbers has successfully demonstrated significant improvements in beta-cell function following a HIIT intervention (Madsen *et al.*, 2015b).

Assessment of efficacy

The primary endpoint for this study is pancreatic beta-cell function assessed during an IVGTT. Thus, the HIIT intervention will be deemed efficacious if participants in the intervention group have a significantly higher beta-cell function than those in the control group, i.e. there is a greater improvement in insulin response to intravenous glucose after the 16-week intervention than after 16 weeks of usual care. Significant difference will be determined using two-way ANOVA (or other more appropriate statistical tests) as outlined above.

The secondary endpoints will provide evidence of the efficacy of the HIIT intervention on inducing improvements in other measures of cardiometabolic health and are listed below:

- Improvement in insulin sensitivity suggested by increased insulin sensitivity index (derived from the IVGTT) and reduced HOMA2-IR
- Improvement in overall glycaemic control – reduced HbA1c, reduced fasting glucose, reduced fasting insulin
- Reduced body weight
- Improved body composition – reduced fat mass and increased lean body mass
- Increased muscle strength and muscle function during electromyography, gait and balance analysis

- Increased fascicle length and greater pennation angle in the vastus lateralis muscle (determined by ultrasonography)
- Improved cardiorespiratory fitness – determined by increased VO_{2max} during CPET

Assessment of safety

Safety of participants will be actively monitored throughout the course of the study. Participants will be contacted regularly through the 16-week study to determine occurrence of adverse events. These will be documented in the participant's case report form and in the trial master file. There will also be a database specifically designated to the documentation of adverse events and safety concerns. This database will be reviewed regularly by the Chief Investigator and Co-Investigators. If there is a high occurrence of adverse events then this will be discussed and considerations made about altering the protocol to counteract this. If the occurrence becomes unacceptably high then the study will be terminated before completion.

Procedures for missing, unused and spurious data

This is a small research study, therefore missing data would have a significant impact on the validity of the results obtained. As such, every effort will be made to ensure the amount of missing data is kept to a minimum. Study visits will be performed by researchers who have a full and complete understanding of every aspect of the study. There will be a detailed proforma with clear instructions regarding the data that are to be collected at each timepoint. In addition, any samples requiring storage prior to analysis will be duplicated and stored in separate freezers.

With these measures in place, we will endeavour to ensure that less than 10% of the data set will be missing. If this is achieved, the data will be analysed using standard statistical techniques as described above. However, if despite these measures there is greater than 10% missing data, this will be discussed directly with the support statistician and the procedure for dealing with this will then depend on the extent of data that is missing. Techniques such as imputation will be considered if required, however if analysis can be performed without the need for such techniques then this would be the preferred option.

If it is not possible to perform an IVGTT in a particular participant (e.g. due to difficulty obtaining vascular access), no data regarding the primary outcome will be collected for that participant. In this situation, data will still be collected for the remaining secondary outcomes during the first visit. Moreover, the participant will be permitted to participate in the 16-week intervention (or control) period and the second visit will be conducted, however without the repeat IVGTT. In order to ensure the target number of participants is reached, with regard to the primary outcome, an additional participant will be recruited for every participant that cannot complete the IVGTT.

Definition of populations analysed

Full Analysis set: All randomised participants, who participated in at least one HIIT session and for whom at least one post-baseline assessment of beta-cell function is available.

Per protocol set: All participants in the Full Analysis set who are deemed to have no major protocol violations that could interfere with the objectives of the study.

ADVERSE EVENTS

Definitions

An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study.

An AE does include a / an:

1. exacerbation of a pre-existing illness.

2. increase in frequency or intensity of a pre-existing episodic event or condition.

3. condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the study.

4. continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

Adverse events most associated with HIIT interventions are musculoskeletal injuries and exacerbation/precipitation of cardiovascular disease (such as angina and acute coronary syndrome). However, meta-analyses of HIIT interventions have repeatedly reported a very low incidence of such adverse events, including in people with T2D (Rognmo *et al.*, 2012; Weston, Wisløff and Coombes, 2014; Cassidy *et al.*, 2017; Hannan *et al.*, 2018). Despite this, investigators will remain vigilant for any signs or symptoms suggesting development of these conditions. In addition, participants will be made aware of associated symptoms and will be instructed to seek medical attention immediately if they were to develop.

An AE does not include a / an:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure may be an AE.

2. pre-existing disease or conditions present or detected at the start of the study that did not worsen.

3. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).

4. disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.

5. overdose of concurrent medication without any signs or symptoms.

A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, having received the intervention, that results in any of the following outcomes:

1. Death

2. A life-threatening adverse event

3. Inpatient hospitalisation or prolongation of existing hospitalisation

4. A disability / incapacity

5. A congenital anomaly in the offspring of a participant

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. In relation to this

specific study, an example would be fracture of a bone directly occurring as a result of performing the HIIT training sessions.

All adverse events will be assessed for seriousness, expectedness and causality. A distinction is drawn between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to the study intervention which makes a causal relationship incompatible or for which other treatments, chemicals or disease provide a plausible explanation. This will be counted as “unrelated” for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to the study intervention which makes a causal relationship a reasonable possibility, but which could also be explained by other interventions, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to the study intervention which makes a causal relationship a reasonable possibility, and is unlikely to be due to other interventions, chemicals or concurrent disease. This will be counted as “related” for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to the study intervention which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as “related” for notification purposes.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

Reporting of adverse events

Participants will be asked to inform the research team of any adverse event occurring. The participant may choose to contact the team themselves, or inform us when a member of the research team performs one of the regular scheduled contacts with the participant. All adverse events will be recorded and closely monitored until resolution or stabilisation, even if it is unlikely that the study intervention is not the cause. The Chief Investigator shall be informed immediately of any adverse events, and shall determine seriousness and causality, in conjunction with other clinically-trained research staff and any treating medical practitioners.

In the event of a pregnancy occurring in a study participant, the participant will be removed from the study as soon as the research team is made aware. Given the nature of the intervention, it is highly unlikely that the involvement in the study will have any effect on the progress of the pregnancy.

All treatment related serious adverse events will be recorded in the trial master file and adverse events database. Unexpected serious adverse events will be reported within the timeframes to the REC as stated below. The Chief Investigator shall be responsible for all adverse event reporting.

Intervention Related SAEs

A serious adverse event that is unexpected in its severity and seriousness and deemed directly related to or suspected to be related to the study intervention shall be reported to the ethics committee that gave a favourable opinion as stated below.

The event shall be reported immediately upon knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the study intervention.
- Take appropriate medical action, which may include halting the trial.
- If the event is deemed related to the study intervention, inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event.
- Within a further eight days, send any follow-up information and reports to the REC.
- Make any amendments as required to the study protocol and inform the REC as required

Participant removal from the study due to adverse events

Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the research team, with final agreement from the Chief Investigator.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the UK Department of Health Policy Framework for Health and Social Care, 2017.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant shall both sign and date the Informed Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS
Case Report Forms

Each participant will be assigned a trial identity code number, allocated at randomisation if appropriate, for use on CRFs other trial documents and the electronic database. The documents and database will also use their initials (of first and last names) and sequential study number, in addition to the study acronym. For example, if a participant is called “Joseph Bloggs” and is the 3rd study participant, the resultant pseudonym will be “JB03”. This is small study so it is unlikely that two participants will have the same initials. If this were to occur, then the second letter of the surname (or subsequent letters) will also be used to distinguish (thus, “JBl03” in the abovementioned example).

All members of the research team will protect the rights of study participants to privacy and informed consent, in accordance with the Data Protection Act 2018. Only the minimum information required for the purposes of the study will be collected and documented in CRFs. CRFs will be stored securely in a locked cabinet and access will be limited to the research team and relevant regulatory authorities. Electronic data will also be stored securely on a database which will be password-protected and kept on a secure, encrypted & dedicated web server provided by the university. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method).

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant’s name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required.

CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the ‘Trial Delegation Log.’

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.
The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Sample Labelling

Each participant will be assigned a trial identity code number for use on the samples, consent forms and other study documents and the electronic database. The documents and database will also use their initials (of first and last names) and sequential study number, in addition to the study acronym, as described above.

Samples for NHS pathology analysis will be labelled in accordance with local NHS procedures.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, laboratory results and records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

The source documents shall include:

- screening documentation
- laboratory test results
- CPET results
- BIA reports
- all progress notes
- questionnaires
- exercise documentation pack

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, and inspection by relevant regulatory authorities (e.g. DH, Human Tissue Authority).

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).
Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

TRIAL CONDUCT

Trial conduct may be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training

received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; accountability of trial materials and equipment calibration logs.

The conduct of the study will be monitored at regular intervals by the Chief Investigator, with regular updates provided by the research team, in particular the Co-Investigator Dr. Oluwaseun Anyiam.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Chief Investigator will take overall responsibility for the monitoring of study data, which will be reviewed at least on a bimonthly basis. This will be performed with the assistance of the Co-Investigators who will assess different aspects of the data generated. There will be an interim analysis of data performed 8-10 months into the study.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the study risk assessment) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by REC as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.
Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

The results of this study will be submitted for publication in at least one high quality peer-reviewed journal for widespread dissemination. The intention is for this to occur within one year of study completion. As this is a pilot study, the aim is to use the findings to inform the development of much larger-scale studies investigating the use of home-based HIIT to facilitate the maintenance of long-term post-VLCD diabetes remission.

USER AND PUBLIC INVOLVEMENT

This study has been developed based on the results of public and patient involvement conducted during the development of previous projects. Feedback from patient groups regarding exercise interventions highlight the commonly cited barriers to engagement in exercise interventions, particularly lack of time and aversion to using gym facilities.

This study has been discussed with the individuals managing the local Path to Remission programmes, and individuals within NHS England. Therefore, study results can be disseminated rapidly through these channels, particularly to key stakeholders involved in the national implementation of the programme. Furthermore, investigators within the research team have good links with the local Diabetes UK patient groups and the Derbyshire Tier 3 Specialist Weight Programme Support Group. These groups may be involved in the dissemination of study results to enable rapid communication among people with T2D.

STUDY FINANCES

Funding source

This study is funded by the Association of British Clinical Diabetologists (ABCD) “Dragons Den” Grant Award 2023.

Participant stipends and payments

All participants will receive a £75 good-will gesture to thank them for their involvement. These will be paid upon completion of the 16-week study. In addition, refreshments will be provided to participants during the study visits. Travel expenses will not be reimbursed, however free parking is available for study participants in the Medical School Building car park.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)____Professor Iskandar Idris_____

Signature:_____

Date: _____

Co- investigator: (name) ____Dr Oluwaseun Anyiam_____

Signature:_____

Date: _____

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