Can a remotely monitored, home-based exercise intervention for individuals with type-one diabetes reduce immune-driven disease activity?

Participant information sheet

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Location(s): 1) Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust; 2) Musgrove Park Hospital, Somerset NHS Foundation Trust; 3) School of Sport and Exercise Sciences, Liverpool John Moors University, 4) Royal Free Hospital, Royal Free London NHS Foundation Trust, 5) East Suffolk and North Essex NHS Foundation Trust

Lead Investigator: Dr Alex Wadley

Name of Researchers: Dr Parth Narendran, Dr Heather Long, Professor Janice Thompson, Dr Robert Andrews, Dr Matthew Cocks, Dr Francesca Di Rosa

We invite you to take part in a research study

You are being invited to participate in a research project. However, before you give consent to participate in the study, it is important that you completely understand why this research is being completed and what will be required of you. Please take time to read through this information sheet. If there are any areas that are not clear, or that you would like more information on, feel free to contact the researchers who will be happy to provide this information for you.

Brief Summary

The aim of this project is to investigate whether a home-based exercise programme can reduce disease activity in patients with recently diagnosed type-1 diabetes (T1D).

What is the study about?

Type-1 diabetes (T1D) is a disease where the body's own white blood cells attack the pancreas, resulting in higher levels of sugar in the blood. If sugar is not removed from the blood, it becomes toxic and results in symptoms of T1D, including increased thirst, fatigue, and frequent urination. Long-term high blood sugar levels cause complications such as eye, kidney and nerve damage, as well as reduced quality of life and life expectancy. At the time of diagnosis, the pancreas of patients with T1D has some remaining function; however, this gradually declines as white blood cells continue to attack the pancreas year by year. Strategies that can reduce the actions of these white blood cells are of huge importance to patients with T1D in managing their health.

Regular participation in exercise is key to supporting health and wellbeing in people with T1D. Regular exercise can cause marked improvements in fitness, life expectancy and psychological well-being. Whilst there is some understanding that exercise improves the health of the pancreas in patients with type 2 diabetes, little is known of the benefits in T1D. Furthermore, there is no work to date addressing how regular exercise can affect white blood cell's attack on the pancreas in patients with T1D.

We would like to explore how exercise uptake early after diagnosis with T1D can reduce the number of white blood cells in blood that can attack the pancreas. To do this, we will take blood samples before and after a popular home-based exercise program (designed for patients with T1D) to determine whether exercise can slow the progression of the disease. With around 70% of people with T1D not meeting the current recommended exercise guidelines, this project seeks to provide novel evidence that exercise can directly lower disease activity in patients with T1D.

Am I eligible for this study?

You could be eligible for this study if you fulfil the following criteria:

- Age: over 18.
- Male of Female
- You were diagnosed with T1D within the last 3 years
- You self-administer insulin as part of a multiple dose injection regime or insulin pump therapy.
- Feel you are able to exercise safely, recognise low blood sugar symptoms (we are defining low blood sugar as 3.5mmol/L), estimate the carbohydrate content of your meals and adjust insulin and carbohydrate doses accordingly.

You may NOT be eligible for this study if you fulfil the following criteria:

- You are pregnant or planning pregnancy
- You currently engage in more than 150 minutes of exercise per week
- Have uncontrolled blood pressure
- Additional health conditions that might put you at risk for this study e.g., heart disease or diabetic complications (kidney, eye, nerve issues) or a history of severe hypoglycaemia requiring third party assistance within the last 3 months.
- Not owning a smartphone/ or having no data plan or access to WiFi.

Please note that if you are unsure on any of the above, please contact the research team and we will help. If you become pregnant during the study you will need to inform the research team and withdraw from the study.

What would taking part involve?

If you agree to take part in the study and meet the inclusion criteria after our initial screening (conducted remotely), you will be asked to sign a consent form and a copy of this information leaflet will be provided to you. You will then be invited to attend your local Clinical Research Facility (CRF) on four separate occasions over a 36-week period. You will be randomly allocated to either a home-based exercise or control group (undertake your usual level of exercise without any extra support from us) between weeks 1-12. Following a 12 week break from the study, you will be allocated to the other group in weeks 24-36. Please see a simplified study schematic on Page 6:

Initial Meeting (30 minute time commitment)

We can arrange an initial meeting, via telephone or video call (depending on your preference), so you can ask any questions you may have about the study. We will also assess your eligibility for the study using two study screening questionnaires. If you wish to take part in the study and are eligible, we will ask you to sign the document using the digital signature tool HELLOSIGN.

Remote screening (30 minute time commitment)

Following this, we need to carry out some additional screening tests to confirm your diagnosis of T1D. We will send you a container in the post alongside a pre-paid envelope addressed to the University of Birmingham. We ask that you fill this with approximately 3 mL of saliva. At this time, we will also ask you to carry out a lateral flow test to confirm that you do not have COVID-19.

DNA material in your saliva sample will be analysed to confirm your diagnosis of T1D and to determine if you have a genetic sequence present in approximately 50% of people. We may then approach you at this point and inform you that you're not eligible for this study. If this is the case, we will ask you to fill out some questionnaires relating to your health-related quality of life and, barriers to physical activity and your levels of physical activity at weeks 1 and 36. Eligible participants will also be asked to fill out these questionnaires at weeks 1, 12, 24 and 36.

Guidance/ coaching before starting each study arm (60 minute time commitment)

We will arrange a meeting via telephone or video call (depending on your preference) to discuss how the exercise and control arm will work in detail. Participants undertaking the exercise intervention arm will be asked to download the training App, Polar Flow. The research team do not own the data recorded on the Polar Flow mobile apps or downloaded to Polar Flow website. The data is owned by POLAR Electro. However, no personal data will be provided to the company as a unique login and password will be created for you using a study code. Furthermore, the Polar Unite watch has no in-built GPS tracking function, hence no information regarding your location will be known at any time. We will provide you with a copy of the privacy policies before consenting to the study. We will then ask for your permission to use the mobile App and website.

The Polar Flow App requires information to be downloaded from your phone to cloud storage. This will use your mobile phone data and as such could cost you money which the research

team will not reimburse. To avoid using your mobile data this process can be done using Wi-Fi.

We will then go through the specifics of the exercise intervention in depth (Coaching Session 1). We will outline which exercise to do, when to do them, how often and how to use the Polar Unite Watch, Polar Flow App and the coaching website. Finally, we will outline some important safety measures to be aware of whilst exercising.

<u>In Person Visits 1-4 (6 hour total time commitment over 36 weeks)</u>

The visits on weeks, 0, 12, 24 and 36 will be identical unless stated below. You will be asked to visit your local clinical research facility (*) on four separate occasions over a 36-week period, each separated by 12 weeks. These visits will last approximately 2 hours on visits 1 and 3 and 1 hour on visits 2 and 4. For all visits, you must be fasted (consume only water, no food from midnight the night before). You will also be asked to refrain from any strenuous exercise for a 48-hour period before each study visit. We will also ask for confirmation of double vaccination against COVID-19, as well as performing screening checks for COVID-19 symptoms prior to each visit.

I. *General Health Assessment*
We will measure your height, weight, waist circumference, resting heart rate and blood pressure.

II. *Clinical Screening*
You will have an appointment with a diabetes doctor to check that you are physically ready to commence the study.

III. *Blood Sampling*
We will take a single blood sample (50mL) on each visit (*). This is equivalent of 5 of the usual sized blood bottles that are taken when you have a blood test at your diabetes clinic appointment. These blood samples will be used for our primary analysis of your white blood cells and also routine clinical measures relating to your diabetes (e.g. HbA1c, cholesterol, glucose and C-peptide).

IV. 14-Days blood sugar monitoring
You will wear a flash glucose monitor to track your blood sugar levels for 14 days after you performed the above measurements. This device uses a small sensor inserted under the skin on your upper arm to check sugar levels throughout the 14-day period. Like the blood sample described above, you will feel a small scratch when the sensor is inserted. On visits 1 and 3, we will insert this and scan the sensor for you. Two weeks prior to visits 2 and 4, we will ask you to insert and scan the sensor yourself using a reader device that we will send you in the post. Both sensors and the reader need to be returned on visits 2 and 4.

V. *Group Allocation*
During visit 1 (week 1), you will be randomised into either the exercise intervention arm or control arm, followed by the opposite study arm on visit 3 (week 24). This is so that you will be included in both arms of the study – the arm where you exercise and the arm where you don't. When you do the exercise arm of the study, you will then be given (or sent in the post) the relevant equipment (i.e. heart rate monitor) and opportunity to ask any questions to the research team. On visits 2 (week 12) and 4 (week 36), you will be asked to return the equipment to the research team.

***** For blood samples taken outside of the Birmingham, blood samples will be posted to the University of Birmingham using Royal Mail Safeboxes within 24 hours. This is a prepaid,

tamperproof box for sending biological samples safely via special delivery. Please note that 50 mL of blood is equivalent to approximately 3 tablespoons.

Exercise Intervention Arm

You will be asked to undertake our validated 12-week home-based exercise programme, which consists of 3 sessions of high intensity intervals per week. You will be given a fitness watch (Polar Unite) and access to a free online training App (Polar Flow). The fitness watch will act as a personal trainer on your wrist, giving you guidance and feedback during exercise on how to complete the planned sessions. The training App will allow you see the entire training programme and monitor your progress. Data recorded by the fitness watch will also be available to research team to help them provide personalised feedback throughout the programme:

1. For weeks 1-2 of the intervention, we will ask participants to:
    - Perform a low intensity warm up for 2-minutes
    - Perform 6 x 1-minute high intensity intervals, interspersed with 1-minute rest intervals (11 minutes). You will be asked to exercise at an intensity that elicits 80% of your maximum heart rate.
    - Total exercise time will be 13 minutes.

2. For weeks 3-4 of the intervention, this will increase to 8 intervals (total exercise time will be 17 minutes).

3. For weeks 5-12 of the intervention, this will increase to 10 intervals (total exercise time will be 21 minutes).

Each interval will use bodyweight exercises, with each interval divided into two different bodyweight exercises performed for 30 seconds with no rest between exercises. You can choose from a selection of 18 exercise pairs (e.g., star jumps, burpees). The research team will provide weekly feedback on compliance with the planned exercise targets. During the first month of the programme you will be asked to provide feedback on your exercise sessions via the training App. The research team will then send a message based on what you did in the session and your feedback. You will be able to reply to these comments. A telephone and/or video call will be arranged between weeks 2-4 to clarify anything that is not clear or discuss the programme in more depth (Coaching session 2). If necessary, your exercise programme will be modified based on these conversations.

Control Arm

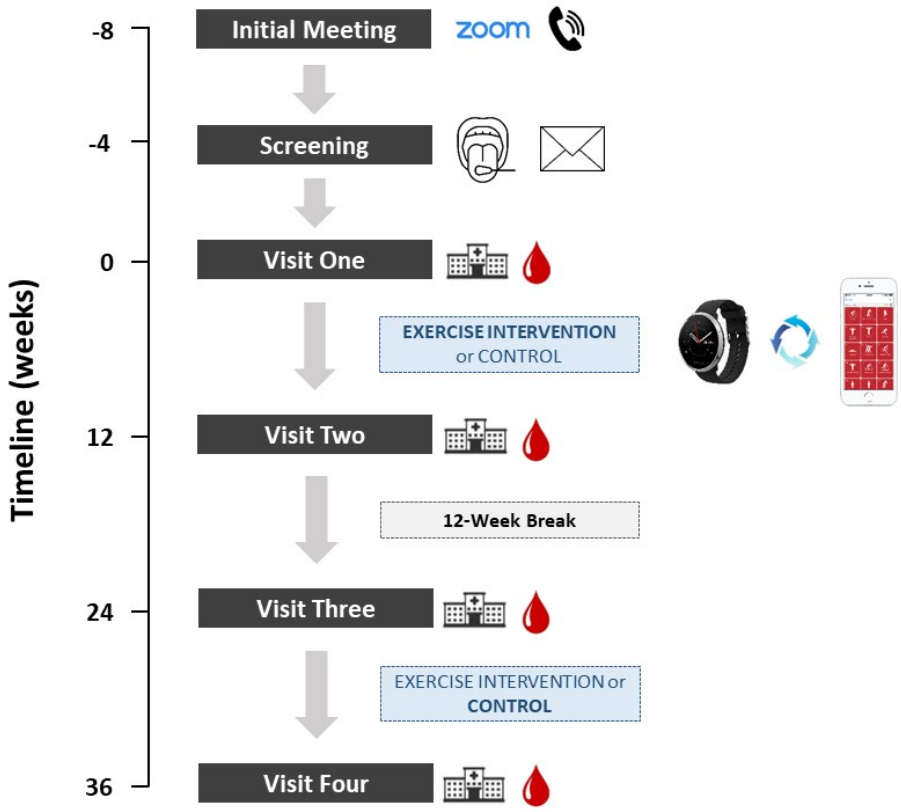
In the control arm of the study, you will not be given any structured advice on the exercise that you undertake, but please continue any normal physical activity you routinely undertake (e.g. walking to work or shops, or any sport you usually do). You will be given a Polar Verity Sense Heart Rate Sensor to wear during any structured exercise sessions that you wear. You will receive no feedback from these sessions from the research team.

Study Completion

Following completion of each study arm, we ask that you please return the necessary equipment (heart rate monitor, wrist-worn activity monitor and flash glucose monitor sensor and reader). A telephone and/or video call will be arranged to discuss your progress with the training programme and how you could continue exercising (Coaching session 3). We will ask you to fill out some short questionnaires about how you found the intervention as well as the

aforementioned questionnaires relating to your levels of physical activity, health-related quality of life and barriers to physical activity.

Simplified Study Design



Do I have to take part in the study?

No. Taking part in this study is entirely voluntary. If you would like to participate, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw will not affect your rights, or any future treatment or service you receive.

What are the possible benefits of taking part?

All participants will receive a £50 Amazon voucher following study completion and travel expenses incurred by site visits can be reimbursed. Participants will also receive training and experience with using our customised exercise intervention for patients with T1D that is coordinated using mobile health (mHealth) technology. We hope this experience will give you confidence to manage the progression of your exercise moving forward. We will measure your general and clinical health, for example blood pressure and heart rate. Once the study has finished, we will provide advice on the best types of exercise to benefit your health and T1D.

What are the possible disadvantages and risks of taking part?

Blood Samples: we will need to briefly insert a small needle into a vein in your arm on four occasions (visits 1-4). As far as discomfort is concerned, there might be a small sting with insertion but otherwise these procedures are not usually painful. There is a very small risk of infection and bruising at the site of insertion. This risk will be much reduced using trained staff and good procedures. The total amount of blood we would take over all four visits is 200 mL, which corresponds to approximately one third of a normal blood donation (*). It is safe to lose this amount of blood, but you should not attend a blood donor session for the next twelve weeks.

* Please note that 200 mL of blood is equivalent to approximately 13 tablespoons.

Exercise:

1. **Fatigue**: You will experience fatigue during the exercise sessions. This is normal and will be short-lived and you should fully recover within hours of the process. However, during exercise there is a very minimal risk of unforeseen heart failure. Although specific figures are not available for people with Type 1 diabetes, the risk of a cardiac event or complication in adults without existing heart disease ranges from 1 in 400,000 – 800,000 hours of exercise. Even in patients with heart disease, who are recognised as high risk, the risk equates to 1 death every 176,000 hours of exercise. As such, the risk is deemed extremely small. You are also free to stop exercising at any point if you feel uncomfortable.

2. **Changes to blood glucose levels**: exercise can make blood glucose levels go up or down. The sort of exercise we are using in this study does not generally cause hypoglycaemia (low blood glucose) but you will be asked to check your blood glucose before and after the exercise, and also several hours after exercise to make sure you are safe. The glucose could be checked by finger prick as well as through any glucose sensor you have (such as a Freestyle Libre). Before you start the intervention, we will provide important safety information regarding **I**nsulin injections, **C**arbohydrate intake, and **E**xercise (ICE).

Could I be excluded from the study?

Yes. You can be excluded from the study at any time point if something happens that affects your eligibility for the study or you are unable to complete the study.

What if we find something unexpected?

There is a chance one of our tests will pick up an unexpected finding. Should this occur we will discuss this with you and send this information to your GP, and we will advise you to speak with your GP.

What happens if something goes wrong on the day of the trials?

All procedures have been included within University of Birmingham Liability insurances and if you are harmed in any way by taking part in this research project your normal rights apply and you may have ground for legal action.

Will my taking part in this study be kept confidential?

We will follow ethical and legal practice and all information about you will be handled in confidence. All data will be labeled with a code, not with your name. Only the research team which is in contact with you has access to the link between code and name of the subject. Data will be anonymised and stored in locked cabinets in the School of Sport, Exercise and Rehabilitation Sciences. The blood samples we collect from you will be stored in freezers in the School of Sport, Exercise and Rehabilitation Sciences to which access is restricted to our research personnel only. Your samples will not be identifiable with your name but with a unique identification number. Your samples will not be sold for profit, used in animal research or shared with non-research organisations, such as the police.

How we will use information about you?

We will need to use information from you for this research project.

This information will include your:

- Name
- Initials
- Contact details
- Date of birth

People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study. As outlined above, with your permission your saliva samples and data will be transferred to the University of Exeter.

Where can you find out more about how your information is used?

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- by asking one of the research team
- by sending an email to a.j.wadley@bham.ac.uk

What will happen to results of this project?

The results of this study are expected to be published in a scientific journal and presented at international conferences, but names of participants will never be published. We will also arrange an informal meeting with all participants with type 1 diabetes who helped with the study so we can tell them what we found.

What will happen to samples remaining at the end of the study?

With your permission, at the end of the study, your blood samples will be stored in a licenced tissue bank at the University of Birmingham to ensure their safe use in the future research. All personal identifying information will be kept separately and may only be accessed by approved personnel. This research may form part of collaborations in the UK or overseas including collaborations with scientists within companies.

Specifically samples:

a) Will not be sold for profit

b) Will not be used in animal research

c) Will not be shared with non-research organisations, such as the police.

Financial reimbursements

Participants will receive a £50 Amazon voucher upon completion of the study. If considerable travel time is needed for each in person study visit, we can also reimburse some travel expenses.

What are my rights?

It is your choice whether or not you wish to take part in this study. If you wish to take part in this study, you will be given this information sheet to read and be asked to sign a consent form. You are reminded that if you decide to take part in the study, you are still free to withdraw from the study at any time without giving a reason. If you withdraw from the study, the data and blood samples already collected will be retained, unless you request for them to be removed within 12 weeks of the first visit.

Who is funding the study and who has reviewed the study?

This study is sponsored and insured by the University of Birmingham and is funded by the **Rosetrees Trust** (Lead investigator – Dr Alex Wadley). The study has been reviewed and approved by an independent Research Ethics Committee (IRAS: 303066).

What if I want to make a complaint?

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact the study investigators who's contact details are available towards the end of this leaflet, in the first instance. If you remain unhappy with their response please contact the Patient Liaison Services (PALS) at your Research Site (Insert PALs contact details here).

Data Protection Notice

University of Birmingham is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. University of Birmingham will process your personal data for the purpose of research. Research is a task that we perform in the public interest. University of Birmingham will keep identifiable information about you for 10 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the study to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at by contacting University's Data Protection Officer at dataprotection@contacts.bham.ac.uk. If you remain unsatisfied, you may wish to contact the Information Commissioner's Office (ICO). Contact details, and details of data subject rights, are available on the ICO website at: https://ico.org.uk/for-organisations/data-protection-reform/overview-of-the-gdpr/individuals-rights/

What happens now?

You will be asked to complete an informed consent form to confirm that you are happy to participate in this study. You will be asked to keep a copy of this information sheet and the signed consent forms. With your permission we will inform your GP about your participation in the study. In this letter we provide them with the results from your baseline blood test (HbA1c, total cholesterol, HDL cholesterol, and triglycerides).

Thank you for your time, and if you want to participate in the study or have any further questions, please feel free to contact any of the investigators listed below. If you wish to discuss this with others, contact your GP.

Contact for further information

Thank you for your time reading this document. If there is anything that is not clear, you would like more information or wish to take part in this study, please do not hesitate to contact:

Dr Alex Wadley (Chief Investigator)

Email: a.j.wadley.bham.ac.uk