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EXTOD-Immune: a randomised controlled trial to investigate whether a remotely monitored, home-based exercise intervention can reduce disease activity in people with type 1 diabetes

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ABSTRACT

Type 1 diabetes (T1D) is a chronic autoimmune disease in which the adaptive immune system targets insulin-producing β-cells of pancreatic islets, leading to dependence on exogenous insulin therapy. Cytotoxic ($CD8^+$) T-cells specific for islet antigens are major players in T1D autoimmunity. Data indicate that regular exercise may preserve β-cell function in people recently diagnosed with T1D, but the role of islet-reactive $CD8^+$ T-cells is unclear. In a randomised crossover design, this study will determine the impact of a 12-week exercise programme on the frequency and proliferative state of islet-reactive $CD8^+$ T-cells in the peripheral blood of 20 adults diagnosed with T1D within the past 3 years. The exercise intervention will consist of three high-intensity interval training sessions per week (6–10 1 min intervals >80% maximum heart rate, with 1 min rest), the duration of which will incrementally increase from 14 to 22 min. Habitual physical activity and diet will be maintained during control and washout periods. At weeks 0, 12, 24 and 36, a fasting blood sample will be collected to quantify the frequency, phenotype and proliferative activity of islet-reactive $CD8^+$ T-cells (primary outcome) and various clinical parameters. Glycaemic control will also be evaluated using 14-day continuous glucose monitoring at the start and end of each study arm. Findings may provide a rationale for conducting large-scale trials to evaluate the implementation of exercise into routine clinical care, particularly for people recently diagnosed with T1D when maintenance of β-cell function is critical to counteract disease progression.
Trial registration number: ISRCTN79006041.

INTRODUCTION

Type 1 diabetes (T1D) is an autoimmune disease characterised by the destruction of pancreatic islets' insulin-producing cells. Around 400 000 people in the UK are currently living with T1D, with incidence rates rising by an estimated 4% every year.[1] People with T1D

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Adults with type 1 diabetes (T1D) are encouraged to engage in 150 min or more of moderate-intensity to vigorous-intensity activity per week due to cardiorespiratory fitness, blood lipid profiles and glycaemic control benefits.
⇒ Recent evidence also indicates that regular exercise may preserve β-cell function in people recently diagnosed with T1D, although the underlying mechanisms remain unclear.
⇒ Cytotoxic ($CD8^+$) T-cells are the key protagonists of β-cell demise in T1D.
⇒ Although regular exercise can exert anti-inflammatory immunomodulation in healthy individuals, its impact on $CD8^+$ T-cell autoreactivity in those with T1D has not been explored.

WHAT THIS STUDY ADDS

⇒ Using peptide-human leucocyte antigen class I tetramer staining coupled with flow cytometry, this study will be the first to evaluate the frequency and proliferative state of islet-reactive $CD8^+$ T-cells before and after a 12-week exercise intervention in people recently diagnosed with T1D.
⇒ Clinical markers of disease progression (eg, haemoglobin A1c, glycaemic control and insulin dose) will also be monitored, and together, these data will determine whether regular exercise can reduce autoimmune disease activity in those with T1D.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ For people recently diagnosed with T1D, maintenance of β-cell function is critical to counteract disease progression.
⇒ Findings from this study will further explain how exercise may protect β-cell function and provide a rationale for implementing regular exercise into routine clinical care to improve patients' quality of life and reduce the cost of T1D to healthcare providers.

are dependent on exogenous insulin therapy for symptom management and mitigation of long-term adverse health outcomes resulting from poor glycaemic control. The most comprehensive analysis estimates that the disease costs the National Health Service (NHS) over £1.5 billion annually.[2]

At the time of diagnosis, many people with T1D present with residual β-cell function, often measured by detectable levels of C-peptide in the circulation.[3] These levels progressively decline within 7 years of diagnosis, reflecting functional β-cell loss, followed by stabilisation.[4] Impaired β-cell function results in compromised metabolic control, increased insulin requirements and a heightened risk of disease complications.[5] Highly differentiated, autoantigen-primed $CD8^+$ T-cells are enriched in insulitis lesions and thus are considered the major protagonists in β-cell destruction.[6] Pharmacological methods to target $CD8^+$ T-cell activation have been explored, with anti-CD3 monoclonal antibody teplizumab recently gaining Food and Drug Administration approval for T1D treatment. However, the timeline for the impact on people with T1D is unclear, as Medicines and Healthcare products Regulation Agency (MHRA) approval in the UK is still pending. Furthermore, the risk of adverse effects and limited long-term success of immunotherapy drugs, including teplizumab, continues to restrict treatment options for many people with T1D due to targeting of non-islet-specific T-cells.[7] Developing cost-effective and self-managed strategies to reduce immune-mediated decline in β-cell function is paramount for people with recent-onset T1D.

To this end, mounting evidence supports the inclusion of exercise in T1D care.[8] In addition to improving aerobic fitness, muscle strength and flexibility, blood lipid profiles and reducing daily insulin requirements, regular structured exercise has reduced all-cause mortality and cardiovascular disease risk in people with T1D.[9] As a result, the American Diabetes Association recommends all adults with T1D engage in 150 min or more of moderate-intensity to vigorous-intensity activity per week.[10] However, many people with T1D fail to reach these guidelines, commonly citing fear of hypoglycaemia and a lack of knowledge on how to manage their condition as major barriers.[11]

The influence of different modes, durations and intensities of exercise on acute and chronic glycaemic control has been explored previously in T1D cohorts. The literature largely supports the notion that high-intensity exercise bouts exhibit a lower incidence of acute hypoglycaemic events than moderate-intensity continuous bouts.[12] Furthermore, over time, supervised and home-based high-intensity interval training (HIIT) interventions have been reported to improve chronic glycaemic control,[13] daily insulin dose[14 15] and cardiorespiratory fitness.[14 16] HIIT also removes commonly perceived barriers to exercise in people with T1D (eg, time-efficiency and cost), with the short duration and the option to complete sessions in a home environment with little to no equipment resulting in high adherence and compliance (95%±2% and 99%±1%, respectively).[14] However, the effect of HIIT on total glycaemic variability has yielded mixed results,[17 18] highlighting the need for further research and the inclusion of continuous glucose monitoring systems.

Direct evidence supporting exercise-induced β-cell preservation in T1D largely comes from studies of rodents. Exercise training has been reported to increase proliferation, preserve morphology and improve insulin production of islet β-cells.[19] These effects extend to the immune system, whereby training can reduce the infiltration of immune cells into pancreatic islets and reduce insulitis by 50%.[20] In humans, following the introduction of exogenous insulin in people with T1D, a 'honeymoon phase' of partial recovery of β-cell function, clinically defined as an insulin dose-adjusted $A_{1C} \leq 9$, is observed.[21] Retrospective case-control data indicate that this period of remission is up to fivefold longer in physically active individuals with T1D compared with those who were sedentary. Moreover, pilot data indicate adults with T1D who engage in regular moderate-to-vigorous exercise may have a delayed decline in β-cell function compared with inactive controls[22] and lower T1D-specific autoantibodies.[23] A recent trial in children with multiple diabetes-related autoantibodies also reported a relationship between higher activity time and lower risk of T1D progression.[24] These data indicate that regular physical activity might protect against loss of β-cell function with disease progression; however, its impact on disease-specific autoimmunity has not been investigated.

Regular exercise induces anti-inflammatory effects at the systemic and tissue level.[25] Notably, exercise training can limit the accumulation of senescent and exhausted $CD8^+$ T-cells in the peripheral blood compartment of healthy individuals[26] and mitigate the contribution of these cells in mediating abnormal glucose homeostasis in adults with type 2 diabetes.[27] Although these data indicate regular exercise can modulate T-cell phenotype, whether these effects are apparent in $CD8^+$ T-cells that specifically drive T1D pathology is unknown. To this end, using peptide-human leucocyte antigen class I tetramer staining coupled with flow cytometry, longitudinal studies in people with T1D have revealed that β-cell-reactive $CD8^+$ T-cells acquired enhanced effector function during the period leading to clinical diagnosis. Interestingly, both individuals with T1D and healthy controls had a similar frequency of islet-reactive $CD8^+$ T-cells in peripheral blood.[28] Cell cycle analysis has also been used to separate actively proliferating cells from resting counterparts, revealing that a subset of people with T1D have a higher frequency of islet-reactive $CD8^+$ T-cells in the S-G2/M phase (termed islet-reactive $CD8^+$ T Double S for T cells in S-phase in Sanguine (T_{DS}) cells) than healthy controls. Moreover, these cells show phenotypic markers associated with highly aggressive effector function.[29] Given the immune modulation induced by regular structured physical exercise, including anti-inflammatory effects and reduction in $CD8^+$ T-cell senescence, evaluation of T-cell

autoimmunity by enumerating changes in islet-reactive $CD8^+$ T_{DS} cells is an important knowledge gap to address.

Aims

Primary: to investigate whether a 12-week home-based HIIT programme reduces the frequency of islet-reactive $CD8^+$ T_{DS} cells in people with recently diagnosed T1D compared with a control period of habitual activity.

Secondary: to determine associations between changes in islet-reactive $CD8^+$ T_{DS} cells and clinical markers of T1D (ie, C-peptide, haemoglobin A1c (HbA1c) and glycaemic variability) after control and exercise periods.

Hypothesis

We hypothesise that compared with 12 weeks of habitual activity, 12 weeks of HIIT will lead to reduced frequency of islet-reactive $CD8^+$ T_{DS} cells and improved clinical outcome measures (glycaemic control, glycated haemoglobin and insulin dose).

METHODS AND ANALYSIS

Trial design

Exercise for Type One Diabetes (EXTOD)-Immune will use a multicentre, randomised controlled crossover design. Participants will complete both study arms (12-week exercise intervention and 12-week control period) separated by a 12-week washout period. The study arm performed first will be randomised. Participants will receive regular remote support and attend four research visits at a local facility (figure 1).

Setting and recruitment

EXTOD-Immune is a prospective study recruiting from multiple UK research sites: University Hospitals Birmingham NHS Foundation Trust, Liverpool John Moores University, Somerset NHS Foundation Trust, Royal Free London NHS Foundation Trust and East Suffolk and North Essex NHS Foundation Trust. The leading route of recruitment will be through secondary care diabetes clinics within the above Trusts, where the majority of newly diagnosed people with T1D are referred for initiation of insulin therapy. Participant identification centres (PICs), including Yeovil District Hospital, Nottingham University Hospitals, North Bristol NHS Trust, Clinical Research Network West Midlands and local general practitioner (GP) practices in the West Midlands area, will also screen primary care records and contact potential participants. Furthermore, recruitment campaigns will be advertised on a study website and social media platforms by the following organisations: Research for the Future, the Type 1 Diabetes Consortium, After Diabetes Diagnosis Research Support System-2 network and Lindus Health. Recruitment opened in April 2022 and is expected to close in July 2025. The registration (ISRCTN79006041) contains the necessary trial information aligned with the WHO Trial Registration Dataset. Recruitment commenced in May 2022, with study completion expected by March 2025.

Participant selection

Research and PIC sites will identify eligible participants whom the medical team will approach. These people and those expressing interest via the website or social media will be connected with the study team at the University of Birmingham. Preconsent eligibility will be assessed using the criteria outlined in table 1, and if eligible, informed consent will be obtained remotely by the University of Birmingham research team using the digital platform Dropbox Sign (online

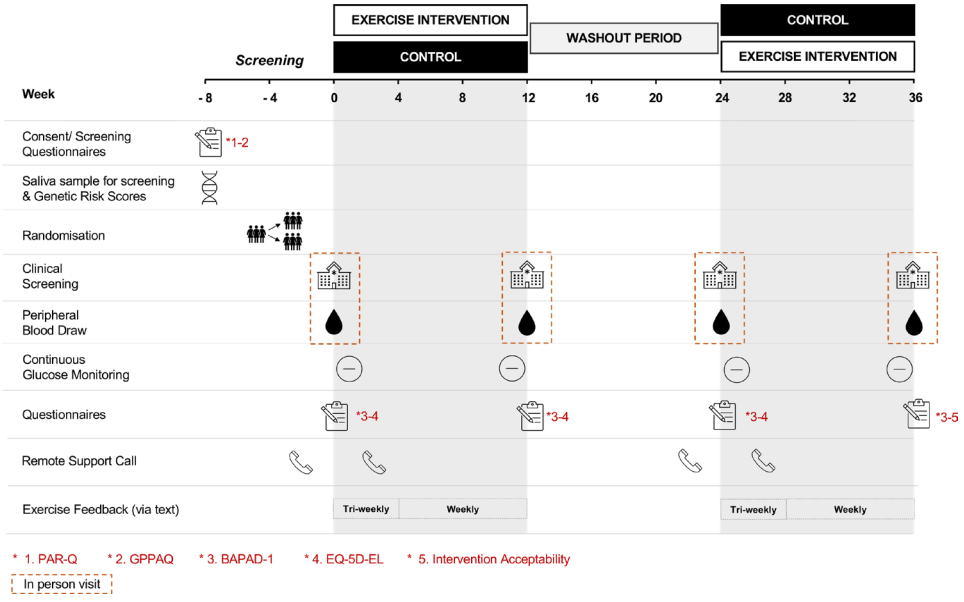

Figure 1 Exercise for Type One Diabetes-Immune study design. BAPAD-1, Barriers to Physical Activity in Type 1 Diabetes; EQ-5D-5L, 5-level EuroQol-5 Dimensions questionnaire; GPPAQ, General Practice Physical Activity Questionnaire; PAR-Q, Physical Activity Readiness Questionnaire.

Table 1 EXTOD-Immune inclusion and exclusion criteria

Inclusion criteria	Aged 18–60 years
	Clinically diagnosed with T1D within the past 3 years
	Self-administering insulin as part of a multiple-dose injection regime or insulin pump therapy
	Able to exercise safety (as determined by participant and lead physician)*
	Participant is able to estimate the carbohydrate content of meals
	Participant is willing to test glucose and adjust insulin and carbohydrate doses accordingly
	Participant is able to recognise hypoglycaemic symptoms before capillary blood glucose falls to 3.5 mmol/L
Exclusion criteria	Uncontrolled blood pressure*
	Pregnancy or planning pregnancy
	Currently engaging in >150 min of exercise per week (self-reported)
	Additional health concerns that prevent safe exercise*
	Unable to provide full informed consent

*Conditions are assessed postconsent.
EXTOD, Exercise for Type One Diabetes.

supplemental file 1). Participant's habitual activity and suitability for the exercise intervention will be assessed during screening using the General Practice Physical Activity Questionnaire (online supplemental file 2) and Physical Activity Readiness Questionnaire (see online supplemental file 3). The participant's GP will be notified of their involvement at this stage. Participants will then provide a saliva sample to determine HLA genotype compatibility for analysis of islet-reactive $CD8^+$ T_{DS} cells (primary outcome). Participants must possess the HLA-A*02 genotype for final enrolment into the study (present in up to 50% of individuals[30]). Individuals who are HLA-A*02 positive and negative will be asked to complete Barriers to Physical Activity in Type 1 Diabetes (BAPAD) (online supplemental file 4) and 5-level EuroQol-5 Dimensions (EQ-5D-5L, online supplemental file 5) (health-related quality of life) questionnaires to obtain data that may help to improve strategies to support exercise management for people with T1D in future studies.

Randomisation

The research team will randomly assign participant identification numbers to a study arm using a pseudo-random number generator with counterbalancing. Allocations will be held by the University of Birmingham research team. Randomisation will be revealed once screening procedures are complete and eligible participants have been assigned a unique study identification number. The nature of the trial prevents participant or researcher blinding. Staff at research facilities will also be informed of allocations.

Outcome measures

Outcome measures for the EXTOD-Immune study are outlined in table 2.

Anthropometrics and blood pressure

Participants will visit their local research facility (Queen Elizabeth Hospital Birmingham, Liverpool John Moores University, Musgrove Park Hospital Taunton, Royal Free Hospital London or Ipswich Hospital) on weeks 0, 12, 24 and 36. Good Clinical Practice-trained site staff with relevant research experience will record the following general health measurements: height, weight, waist circumference (taken in the area between the ribs and iliac crest), hip circumference (at the level of maximum width of the buttocks), blood pressure, pulse rate. The participant's current daily insulin dose will also be recorded at each visit.

Blood sampling

At each research visit, a 50 mL venous blood sample will be collected; 40 mL collected in sodium heparin vacutainers, 6 mL in EDTA vacutainers and 4 mL in serum-activated vacutainers. All samples collected at the Queen Elizabeth Hospital Birmingham will be directly transported to the University of Birmingham and processed immediately. Isolated EDTA plasma and serum will be stored at −80°C, and peripheral blood mononuclear cells (PBMCs) isolated from sodium heparin blood will be stored overnight at −80°C and then transferred to liquid nitrogen for long-term storage. For all other research sites, EDTA and serum bottles will be processed and stored (−80°C) on-site. These samples will be shipped to the University of Birmingham on dry ice for analysis once recruitment has closed. Sodium heparin tubes collected at non-local sites will be sent at room temperature using Royal Mail Safeboxes (Special Delivery Guaranteed) to the University of Birmingham and delivered within 24 hours. As above, isolated PBMCs will be stored overnight at −80°C and then transferred to liquid nitrogen.

Table 2 Parameters measured, and tests conducted throughout EXTOD-Immune

Measured	Measurement strategy	Outcome
Primary		
Immunology	Fasting blood collection at research visits	Enumeration of circulating immune cell subsets, notably islet-reactive $CD8^+$ T_{DS} cells
Secondary		
Exercise adherence and compliance	Mobile health technology (heart rate monitor and fitness watch)	1. Device wear time 2. Number of planned sessions completed 3. Duration of session 4. Number of HIIT intervals completed 5. Exercise intensity via heart rate measurement
Habitual physical activity	Mobile health technology (heart rate monitor only)	1. Number of sessions completed 2. Exercise intensity via heart rate measurement
Anthropometrics	Site staff at research visits	1. Height and weight 2. Hip and waist circumference
Blood pressure	Site staff measure at research visits	1. Systolic and diastolic blood pressure 2. Pulse rate
Clinical measures	Site staff measure at research visits	Insulin dose
Blood biochemistry	Fasting blood collection at research visits	1. Haemoglobin A1c 2. C-peptide 3. Autoantibody titre
Saliva analysis	Participant collects and posts sample to the research team	Diabetes Genetic Risk Score[34]
Glycaemic control	14-day continuous glucose monitoring	1. Device wear time 2. Mean glucose 3. Glycaemic variability (%CV and SD) 4. Time above range (L1 >10 mmol/L, L2 >13.9 mmol/L). 5. Time in range (3.9–10.0 mmol/L) 6. Time below range (L1 <3.9 mmol/L, L2 <3.0 mmol/L) 7. Number of hypoglycaemia and hyperglycaemia episodes 8. Area under the curve
Participants' opinions	Self-reported questionnaires	1. Barriers to Physical Activity in Type 1 Diabetes Questionnaire 2. Health-Related Quality of Life Questionnaire (EQ-5D-5L) 3. Acceptability of the intervention (completed at week 36 only)

CV, coefficient of variation; EQ-5D-5L, 5-level EuroQol-5 Dimensions questionnaire; EXTOD, Exercise for Type One Diabetes; HIIT, high-intensity interval training; T_{DS}, T Double S for T-cells in S-phase in Sanguine.

Glucose monitoring

Libre Pro IQ (FreeStyle Libre Pro, Abbott Diabetes Care, Alameda, California, USA) continuous glucose monitor (CGM) will be provided and worn by participants four times. Each CGM will record interstitial glucose concentrations at 15 min increments for 14 days (weeks 0–2, 10–12, 22–24 and 34–36). Standardised metrics for assessing glycaemic control will be recorded.[31]

Participant questionnaires

Before each research visit, participants will complete two questionnaires (see online supplemental material)—BAPAD and EQ-5D-5L—to capture changing opinions on physical health and the barriers preventing the uptake or adherence of an exercise programme. At the end of the study, an additional open-ended feedback questionnaire will be completed to assess the acceptability of the intervention (online supplemental file 6).

Mobile health technology

Mobile health technology will be used to remotely monitor participants' exercise sessions. Throughout the control arm, participants will be provided with a Polar Verity Sense optical heart rate monitor (Polar Electro, Finland), linked via Bluetooth to the Polar Flow mobile app and asked to record any structured physical activity. For the exercise intervention, participants will be provided with a Polar Verity Sense heart rate monitor and

Table 3 EXTOD-Immune HIIT programme

Week of exercise intervention	Exercise intervals per session	Total duration (min/week)
0–2	6	42
3–4	8	54
5–12	10	66

Paired exercises
1. Mountain climbers+squat touches
2. Floor jacks+get ups
3. Squat thrusts+elbow to knee
4. Split squats+jogging boxers
5. Clapping jumping jacks+jogging on the spot
6. Jogging with high knees+squat jumps
7. Spotty dogs+X jumps
8. Jump overs+jumping jacks
9. Tuck jumps+burpees

During the exercise arm, participants will complete a 12-week HIIT programme. The number of exercise intervals within a training session will increase in three defined stages. Exercise intervals will consist of two exercises, lasting 30 s each. Examples of paired exercises are listed.
EXTOD, Exercise for Type One Diabetes; HIIT, high-intensity interval training.

a Polar Unite fitness watch (Polar Electro) linked via Bluetooth to the Polar Flow mobile app. Participants will be encouraged to wear the fitness watch as much as possible and the heart rate monitor during structured exercise sessions. Devices will be collected by the research team at the end of each study arm; therefore, participants will not have the technology for the washout phase.

Remote support calls

Before the start of each study arm (before weeks 0 and 24), participants will attend a video call hosted by a member of the research team to understand study procedures and learn how to use the mobile health supported equipment. Participants will have a second support session 3–4 weeks into the programme during the exercise intervention to evaluate their progress.

Exercise intervention

Based on data presented by Scott *et al*,[14] the EXTOD-Immune exercise intervention will consist of a 12-week HIIT programme, virtually monitored by the researchers using mobile health technology. Three bodyweight HIIT sessions are to be performed weekly, each comprising a 2 min warm-up of jogging on the spot. The sessions will be followed by a series of 1 min bodyweight exercise intervals interspersed with 1 min passive rest intervals. It is recommended that two bodyweight exercises, each lasting 30 s, are performed continuously within each interval (table 3). Participants will have access to support videos demonstrating how to perform paired exercises. The number of intervals will increase throughout the programme (table 3). Participants are expected to work at 60%–70% of their maximum heart rate (HR_{max}) during the warm-up and >80% during exercise intervals. Preset exercise sessions will be accessible via the Polar Flow app and the Polar Unite fitness watch will provide visual and haptic alerts on performance in real-time. Participants will also be encouraged to leave written feedback via the Polar Flow app and to self-assess the intensity of each session by rate of perceived exertion as defined by Borg's CR-10 scale.[32] Adherence and compliance with the training programme will be monitored remotely using mobile health technology. Compliance with each prescribed HIIT session will be defined as performing the number of prescribed intervals and reaching 80% HR_{max} by the final interval. Over the 12-week intervention, adherence will be defined as completing at least 80% of the prescribed sessions. Participants will receive regular personalised feedback and support on compliance and adherence throughout the intervention via text from the University of Birmingham research team. Feedback messages will be sent after each session for 4 weeks and then weekly for 8 weeks.

Control period

Throughout the control arm of the EXTOD-Immune study, participants will be encouraged to maintain their usual diet and habitual activity. Participants will be asked to record any structured exercise using the provided Polar Verity Sense optical heart rate monitor. Moderate-to-vigorous physical activity data will be collected, but participants will not receive any feedback on recorded activity.

Washout period

Throughout the washout period of the EXTOD-Immune study, participants will be encouraged to maintain their usual diet and habitual activity. No data on physical activity will be collected during this time.

Biological analysis

Major histocompatibility complex (MHC) tetrameric complexes coupled with multicolour flow cytometry will be used to phenotype immune cell subsets from thawed PBMC samples. Immunoassays will be used to quantify HbA1c level and autoantibody titre from plasma and sera samples. Colleagues at the Department of Clinical and Biomedical Sciences, University of Exeter, UK will complete diabetes risk scoring.

STUDY MONITORING AND DATA COLLECTION

Medical management and safety

All participants will be self-administering insulin as part of a multiple-dose injection regime or insulin pump therapy to help glycaemic control. Participants are advised to monitor their blood glucose levels before and after exercising (data not collected) and to speak to their healthcare practitioner for further information about carbohydrate consumption and insulin dosage surrounding exercise. The study team will regularly contact participants to minimise injuries and hypoglycaemia episodes and address

any concerns. Any adverse events or serious adverse events will be logged and reviewed by the research team and then referred to the local medical team.

Ancillary care

Participants experiencing harm due to their trial participation will be covered. If any issues that impact participants' mental health and well-being are raised, we will signpost them to relevant mental health services (Samaritans or MIND) and recommend discussing these matters with their GP or diabetologist.

Data management

Data management with regard to the collection, storage, processing and disclosure of personal information will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018. Data will be stored in line with the University of Birmingham's policy at the termination of the project and will be kept securely for 10 years following completion.

Study monitoring

Any monitoring activities will be reported to the Study Sponsor and Clinical Research Compliance Team at the University of Birmingham, and any issues noted will be followed up on to resolve. Additional internal quality checks may be triggered, such as poor data quality, low protocol deviations or excessive participant withdrawals or deviations. If an internal quality check is required, the Clinical Research Compliance Team at the University of Birmingham will contact the site to arrange a date for the proposed visit. It will provide the site with written confirmation. The principal investigator will permit trial-related monitoring, quality checks, audits, ethical reviews and regulatory inspection(s) at their site, providing direct access to source data/documents. The principal investigator will comply with these visits and any required follow-up. Sites are also requested to notify the Trials Office of any MHRA inspections. A steering committee involving the research team, clinical staff and people with T1D will meet regularly to ensure the trial is conducted and discuss appropriate ethical amendments.

Statistical analysis plan

The effect of study arm order and measurement period on the primary (islet-reactive $CD8^+$ T_{DS} cells) and clinical outcome measures (C-peptide, insulin dose, glucose levels and HbA1c) will be modelled using a mixed effects model, with participant ID as a random effect. If a

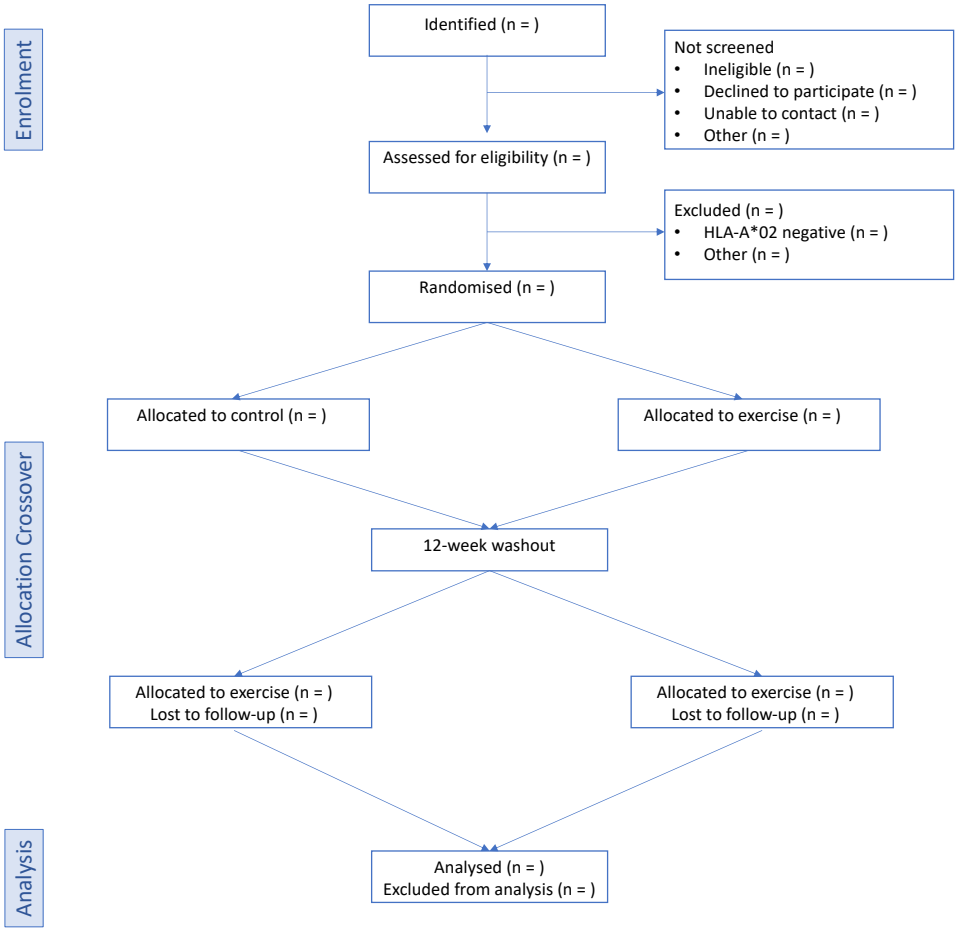

Figure 2 Consolidated Standards of Reporting Trials diagram reflecting the flow of participants through the Exercise for Type One Diabetes-Immune study.

statistically significant order effect is found (p<0.05), this will be reported but not adjusted for in subsequent analysis. Significant period effects will also be reported and will be adjusted for. The normality of residual data will be tested using the Shapiro-Wilk test, and values that do not fulfil test assumptions will be considered for transformation. Mean±SD (or summary statistics if appropriate) will be reported for all primary and secondary outcomes, and statistically significant paired differences will be reported ±SD with 95% CI.

Sample size

This study aims to recruit 20 participants. Given the novelty of the work, a formal power calculation is not appropriate. The sample size was estimated based on previous studies reporting differences in islet-reactive $CD8^+$ T-cells between people with T1D (n=11) and healthy controls (n=10),[29 33] and accounting for typical dropout rates from past clinical exercise interventions (≈15%–20%).[14 22] Recruitment data will be presented in a Consolidated Standards of Reporting Trials diagram (figure 2), and demographic data will be described in summary statistics.

Ethics and dissemination

Favourable ethical opinions were given by Newcastle and North Tyneside Research and Ethics Council (21/NE/0211), Health Research Authority and Health and Care Research Wales. Guidelines from The International Conference on Harmonisation of Good Clinical Practice and the Declaration of Helsinki will be conformed to. The findings of this study will be disseminated at conferences and published in peer-reviewed journals.

Patient and public involvement

People with T1D were invited to review the study design and participant-facing documents (ie, participant information sheet). Feedback was generally positive, with many highlighting the inclusion of regular support sessions as an attractive feature of the study. People with T1D and the public will also be involved in recruiting and disseminating findings where appropriate.

DISCUSSION

To the authors' knowledge, EXTOD-Immune is the first randomised, crossover, controlled trial, which will examine the peripheral blood frequency of islet-reactive $CD8^+$ T_{DS} cells before and after a 12-week HIIT programme and control period in people recently diagnosed with T1D. A target of 20 individuals will be enrolled in the study, a sample size that reflects the challenges faced when recruiting people recently diagnosed with T1D who are also over 18 years of age. This study has also adopted a remotely supervised approach to exercise, which has previously been demonstrated to be equally effective in promoting adherence compared with laboratory-supervised exercise programmes.[14] This methodology will reduce barriers to exercise participation and will be economically viable for people with T1D and healthcare professionals in the real world. Findings from this study will provide insight into the protective mechanisms exercise mounts against autoimmune disease and add to the growing evidence base assessed by clinicians to advise people with T1D on the safest and most beneficial exercise modalities for managing their short-term and long-term health, respectively.

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Contributors AJW conceived the study, and together with PN and MC designed the protocol. PN and RA provided clinical expertise. FDR and HML advised on immunological techniques and analysis, and KH and MC provided resources and support with exercise procedures. MQ will coordinate the project and collect and analyse the data. MQ and AJW are equal guarantors and drafted the current manuscript using Standard Protocol Items: Recommendations for Interventional Trials guidelines. All authors approved the final version. The present and future associated manuscripts will not involve professional writers or artificial intelligence. The trial will be sponsored by the University of Birmingham who will oversee but not have authority over study design; collection, management, analysis and interpretation of data or writing of publications.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the 'Study monitoring and data collection' section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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