ISRCTN10203365 https://doi.org/10.1186/ISRCTN10203365

Investigating and optimising physical function with weight loss

Submission date	Recruitment status	[X] Prospectively registered
13/07/2024	Recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
18/09/2024	Ongoing	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
18/09/2024	Nutritional, Metabolic, Endocrine	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
This study investigates different weight loss strategies for individuals living with overweight and obesity and the effect they have on people's ability to function in everyday life. The different weight loss strategies include drugs, diet and exercise. It is known that people living with overweight and obesity can find daily tasks such as standing up from a chair or lifting shopping more difficult than a person of a healthy weight. If individuals can be helped to lose weight, this might improve their ability to complete daily tasks and could improve their quality of life, as well as other health-related outcomes.

Who can participate?
Adults aged between 18 to 75 years old, with a body mass index (BMI) greater than 30 kg/m2 or a BMI between 27.0 and 30.0 kg/m2 with at least one of the weight-related risk factors (such as high blood pressure). Individuals must be able to walk without assistance and be weight stable for at least 90 days before the study starts.

What does the study involve?
There are three initial cohorts:
1. Those aged between 18 and 44 years
2. Those aged between 45 and 75 years
3. Those with a diagnosis of long COVID
This is an adaptive platform trial, which means interventions may come and go depending on how well they are working. Because of this, there is no set timeline for how long the study will last. Initially, the plan is to conduct the study until September 2029. Participants will be randomised to either usual care or a weight loss intervention (one of four initially). These interventions will last for 24 weeks, with an option to continue afterwards.

What are the possible benefits and risks of participating?
Participants will be under the care of a doctor throughout the study and will receive close monitoring of their health. If they are allocated to an intervention group, they may lose weight and feel healthier generally. There are often long-term health benefits from maintaining weight loss. The study team will review their physical function, body fat, calorie requirements, fitness levels and heart health results with them after the study is completed. By taking part in this

research, participants will contribute to new scientific understanding of the health benefits of different weight loss strategies. The results could lead to improved medical treatments and programmes in the future.

Venepuncture - this will need to be performed at each of the core study visits: Visit 0 (screening and familiarisation), Visit 1 (baseline), Visit 3 (week 12), Visit 4 (week 24), Visit 5 (optional week 52) and Visit 6 (optional week104). This is to obtain the necessary blood samples. This procedure can be associated with mild to moderate pain and discomfort depending on the ease of identifying a suitable vein. The procedure will be performed by highly trained research staff using aseptic techniques and the latest devices. The comfort of the participant will be considered at all times and every attempt to make the procedure less painful (e.g. ensuring vein is identifiable by use of tourniquet, squeezing of fist, lowering forearm, putting hand in warm water). Their right to withdraw from the study or refuse the intervention will be respected at all times.

Indirect calorimetry - this will be performed using a ventilated mask device. Generally, this procedure is well tolerated. However, in a few participants, it may be associated with claustrophobia. The procedure will be clearly explained to the participant before it occurs and the right to withdraw at any time will be maintained.

Body composition will be assessed using Dual Energy X-ray Absorptiometry (DEXA) by a fully qualified technician. Although DXA uses X-rays, this is at a very low dose and any risks are negligible. Female participants under 55 years of age will be asked to have a urine pregnancy test before the scan. They will also be asked about pregnancy status and asked to sign a declaration of pregnancy status form before having a DEXA scan. Any participant at risk of being pregnant will not be scanned.

Muscle Biopsy - The administration of local anaesthetic may cause mild discomfort, and there is a small risk of haemorrhage or infection at the site of the biopsy. The area may ache for a few hours afterwards (painkillers will be available). In some cases, it can cause bleeding and bruising that can last several weeks and may restrict mobility and the ability to drive. Following the local anaesthetic the procedure is not painful, though the site of the biopsy may ache for a day. Analgesia will be offered following a biopsy. All biopsies will be performed by a doctor who has been trained and has experience with the muscle biopsy procedure.

Attendance at multiple study visits - participants will be required to attend five core study visits. All reasonable attempts will be made to ensure that attendance is not associated with too much disruption to the participant's lifestyle. Reimbursement will be provided upon receipt of a valid car parking ticket.

Participants will be arriving for the core study visits having fasted the night before, in preparation for the fasting blood tests at these core study visits. This will be following consent which will be taken at the screening visit. To ensure participant safety and avoid episodes of hypoglycaemia, the participant will be monitored closely by the clinical team on the days of the study visits they are expected to fast.

Low-energy diets can lead to symptoms like constipation, dizziness, fatigue, thirst, and/or headache in some people taking part. Trained dietitians and study clinicians will monitor participants throughout the study and will help manage side effects if they arise. These side effects tend to get better with fibre-based laxatives and time. It is also important to drink as much water as needed when on the diet.

With exercise, there are risks of injury to joints, bones, and muscles. The supervisor will work with participants to exercise as safely as possible. Exercise may also lead to fatigue and dizziness in some cases. Again, over time these should improve.

Tirzepatide is approved for weight loss, however, all medications have some unwanted side effects. Not everybody gets them, and these will be explained by the doctor before consent. The most common side effects with Tirzepatide are feeling nauseated, loose and frequent stools, throwing up, loss of appetite, indigestion, heartburn, feeling tired (fatigue), hard or infrequent stools, passing gas, bloating, belching, stomach pain or discomfort, low blood sugar and injections site reaction (such as redness, irritation, itching, swelling or rash). The study team will advise the participants to maintain adequate fluid hydration to reduce the risk of volume depletion. We will monitor participants for adverse effects and address these accordingly.

Where is the study run from?
This trial will be conducted within the Leicester Diabetes Centre (University Hospitals of Leicester NHS Trust) and Diabetes Research Centre (University of Leicester) which are jointly situated at the Leicester General Hospital. Loughborough University will act as a site for one sub-study.

When is the study starting and how long is it expected to run for?
July 2024 to September 2029

Who is funding the study?
National Institute for Health and Care Research (NIHR)

Who is the main contact?
Dr Gregory Biddle, Diabetes Research Centre, Leicester General Hospital, gjhb2@leicester.ac.uk

Contact information

Type(s)
Principal Investigator

Contact name
Prof Melanie Davies

Contact details
Diabetes Research Centre, Leicester General Hospital
Leicester
United Kingdom
LE5 4PW
+44 (0)116 258 6481
melanie.davies@uhl-tr.nhs.uk

Type(s)
Principal Investigator

Contact name
Dr Dimitris Papamargaritis

Contact details

Diabetes Research Centre, Leicester General Hospital, Leicester
Leicester
United Kingdom
LE5 4PW
+44 (0)116 258 6481
Dimitris.Papamargaritis@uhl-tr.nhs.uk

Type(s)
Scientific

Contact name
Prof Thomas Yates

Contact details
Diabetes Research Centre, Leicester General Hospital
Leicester
United Kingdom
LE5 4PW
+44 (0)116 258 8572
ty20@le.ac.uk

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1009390

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
0973, IRAS 1009390

Study information

Scientific Title
Investigating and optimising physical function with weight loss: a multi-arm open-label adaptive platform trial

Acronym
The OPAL Trial

Study objectives
To investigate the efficacy of newer generations of weight loss therapies and equivalent dietary-induced weight loss +/- exercise on physical function (incremental shuttle walk test) in people living with obesity.

Key secondary objectives are the difference between intervention groups and control at 12 weeks and 24 weeks, and continuation or initiation of therapy up to 52 weeks and 104 weeks:
I. Cardiorespiratory fitness, lower-body strength, handgrip strength and other measures of physical function
II. Body composition, including weight, waist circumference (WC), body mass index (BMI), fat mass (FM), appendicular and whole-body lean body mass (LBM), and bone mineral density (BMD).
III. Muscle architecture
IV. Resting energy expenditure
V. Fasting glucose, insulin and lipid profile
VI. Glycaemic control
VII. Blood pressure
VIII. Diet
IX. Accelerometer measured physical activity, sedentary behaviour and sleep
X. Sleep quality
XI. Patient-reported outcomes (PROMS)
XII. Cognitive function
XIII. Fasting skeletal muscle metabolic and inflammatory signalling pathways*
XIV. Male fertility*
XV. Brain function*
*no measurement at 12, 52 or 104 weeks

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 13/09/2024, East Midlands - Derby Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 1048 154; derby.rec@hra.nhs.uk), ref: 24/EM/0174

Study design
Open-label prospective adaptive individually randomized controlled platform trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Efficacy

Participant information sheet

Health condition(s) or problem(s) studied
Overweight or obesity

Interventions

There are initially five study arms; usual care, low-energy diet, Tirzepatide, low-energy diet with exercise and Tirzepatide with exercise. As this is an adaptive platform trial, interventions may be added or removed as the evidence develops. If this occurs, this record will be amended accordingly. Participants are split into three separate cohorts (younger adults [18-44 years], middle-to-older adults [45-75 years] and long COVID). Each cohort is eligible for a different number of arms. The younger cohort is eligible for all five, the middle-to-older cohort is eligible for all arms except the low-energy diet with exercise, and the long COVID cohort is only eligible for arms without exercise. Randomisation to one of five, four or three arms respectively will be conducted using a sealed envelope in an equal ratio (1:1:1:1:1, 1:1:1:1, 1:1:1).

Usual care participants will receive usual clinical care as per NHS care delivery practice. In addition, participants will receive general advice on weight loss and healthy living, similar to what is supplied within the NHS as per routine care, during a one-off counselling session with a dietitian.

Low-energy diet participants will receive a total meal replacement intervention using meal replacement products totalling 800-900kcal/day (30% protein, 50% carbohydrate and 20% fat) for up to 20 weeks or if a BMI of ≤22kg/m2 is reached. Should a BMI of ≤22kg/m2 be achieved before 20 weeks, an additional visit with the dietary team will be arranged, during which a person-centred and individualised approach will be used to plan food reintroduction aimed at weight maintenance. Food reintroduction will occur between weeks 20 and 24 (earlier if a BMI of ≤22kg/m2 is achieved) and will include tapering the meal packs while reintroducing foods to target maintenance of the weight loss rather than continued active weight loss. The speed of food reintroduction and tapering of meal replacement products will be agreed upon individually with each participant.

Tirzepatide participants will be prescribed Tirzepatide (Mounjaro®) at 2.5 mg once weekly for 4 weeks, then increased to 5 mg once weekly for at least 4 weeks. If tolerated, the dose of Tirzepatide will continue to increase in steps of 2.5 mg at intervals of at least 4 weeks, with a maximum dose of 10 mg reached by week 12 at the earliest. If at any point during the trial, a BMI of ≤22kg/m2 is reached, the recommended energy intake and/or dose of Tirzepatide may be recalculated to achieve weight maintenance, rather than further weight loss. Tirzepatide will be dispensed in four-week blocks unless otherwise advised by the study clinician.

The low-energy diet with exercise participants will follow the same procedures as described for those in the low-energy diet arm, with the addition of structured exercise. During the first 12 weeks, individuals will undertake progressive, combined (aerobic and resistance) exercise training. Two supervised sessions per week will combine an aerobic component with a resistance training component. The third session will be ‘aerobic only’, which participants can opt to perform at home or another site, although exercise at the study facility will be encouraged, particularly during the early stages of the intervention. Regardless, participants will be asked to maintain their usual daily activities on non-exercise days. Broadly, the exercise intensity and duration will be increased as tolerated and the end target duration for each session is 60 minutes. During weeks 13 to 24, the focus of the intervention will be on maintaining compliance with the progress made during weeks 1 to 12. The sessions will continue to include the same combination of aerobic and resistance exercises. To support compliance, access to the Leicester Diabetes Centre exercise facilities will be available and encouraged, with participants able to book preferred times/dates with the research team. At least one supervised session per week will remain, with two sessions undertaken in a home-based or community-based exercise facility. Home-based resistance exercise will be facilitated by resistance bands.

Tirzepatide with exercise participants will follow the same procedures as described for those in the Tirzepatide arm, with the addition of structured exercise (following the same exercise procedures outlined in the diet with exercise arm).

Intervention Type
Drug

Pharmaceutical study type(s)
Pharmacodynamic, Dose response, Therapy

Phase
Phase II

Drug/device/biological/vaccine name(s)
Mounjaro [Tirzepatide]

Primary outcome measure
Physical function measured using meters covered during the incremental shuttle walk test at baseline and week 24

Secondary outcome measures
The following secondary outcomes will be measured at baseline, and 12, 24, 52 and 104 weeks unless otherwise specified:
1. Physical function measured using meters covered during the incremental shuttle walk test
2. Cardiorespiratory fitness measured using maximal exercise test
3. Lower limb strength measured using BIODEX
4. Physical function measured using the Short Physical Performance Battery (SPPB)
5. Physical function measured using handgrip strength
6. Physical function measured using the World Health Organisation Disability Assessment Schedule (WHODAS 2.0)
7. Frailty measured using Fried's Frailty Phenotype (FFP)
8. Fat mass, appendicular and whole-body lean body mass (LBM), and bone mineral density (BMD) measured using DEXA
9. Body composition measured using waist circumference, body weight, height and body mass index (BMI)
10. Muscle architecture measured using ultrasound
11. Resting energy expenditure measured using indirect calorimetry
12. Glycemic control measured using fasting glucose and insulin measured through venous blood sampling
13. Glycemic control measured using continuous glucose monitoring
14. Dyslipidaemia measured using a lipid profile assessed through venous blood sampling.
15. Blood pressure measure using an automated sphygmomanometer
16. Diet measured using a 24-hour diet recall interview and Diet Quality Questionnaire (DQQ)
17. Physical activity measured using a wrist-worn accelerometer, general practice physical activity questionnaire (GPPAQ), physical activity vital signs (PAVS), and international physical activity questionnaire (IPAQ)
18. Sedentary behaviour measured using a wrist-worn accelerometer, general practice physical activity questionnaire (GPPAQ), and international physical activity questionnaire (IPAQ)
19. Sleep measured using a wrist-worn accelerometer
20. Sleep quality measured using the Pittsburgh sleep quality index, self-reported sleep, and

wrist-worn accelerometer
21. Anxiety and depression measured using the Patient Health Questionnaire Anxiety-Depression Scale (PHQ-ADS)
22. Breathlessness measured using the Modified Medical Research Council Dyspnoea Scale (mMRC)
23. Somatic symptoms measured using the somatic symptom scale-8 (SSS-8)
24. Quality of life measured using the European Quality of Life -5 Dimensions (EQ-5D-5L) and the 36-item Short Form Survey Instrument (SF-36)
25. Cognitive function measured using the Montreal Cognitive Assessment and Visual Sensitivity Test
26. Muscle metabolic and inflammatory signalling pathways measured using muscle biopsies at baseline and week 24 only (sub-study)
27. Sperm count measured using semen analysis at baseline and week 24 only (sub-study)
28. Testicular size measured using Orchidometer at baseline and week 24 only (sub-study)
29. Male sexual health measured using the IIEF-15 Sexual health questionnaire at baseline and week 24 only (sub-study)
30. Oestradiol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, thyroid-stimulating hormone (TSH), Free T4 and Inhibin B measured using venous blood sampling at baseline and week 24 only (sub-study)
31. Brain function measured using functional magnetic resonance imaging (fMRI) scan at baseline and week 24 only (sub-study)

Overall study start date
10/07/2024

Completion date
01/09/2029

Eligibility

Key inclusion criteria
Master Inclusion Criteria:
1. BMI of ≥ 30.0 kg/m2
OR
2, BMI ≥ 27 to <30.0 kg/m2 (with at least one of the following weight-related comorbidities or risk factors: hypertension, dyslipidaemia, prevalent or previous cardiovascular disease (e.g., stable heart failure), elevated HbA1c (5.7 - 9.9%), polycystic ovary syndrome, history of gestational diabetes, taking hypertensive medication or taking lipid-lowering medication.
3. Weight stable for at least 90 days before screening (self-reported < 5kg change in body weight)
4. Able and willing to give informed consent
5. Able to understand written and spoken English
6. Able to walk without assistance

Younger age cohort
Additional criteria that outline inclusion for the younger cohort:
18 to 44 years of age at screening (Visit 0), inclusive

Middle-to-older age cohort
Additional criteria that outline inclusion for the middle-to-older cohort:
45 to 75 years of age at screening (Visit 0), inclusive

Long COVID cohort
Additional criteria that outline inclusion for the long COVID cohort:
1. 18 to 75 years of age at screening (Visit 0), inclusive
2. Clinical diagnosis of long COVID with ongoing care, assessed by a long COVID service.
3. Offered long COVID rehabilitation or >6 months post-completion of long COVID rehabilitation.

Exception from the master inclusion/exclusion for the long COVID cohort (these criteria do not apply to this cohort):
1. BMI ≥ 27 to <30.0 kg/m2 (with at least one of the following weight-related comorbidities or risk factors: hypertension, dyslipidaemia, cardiovascular disease (e.g., stable heart failure), elevated HbA1c (5.7 - 9.9%), polycystic ovary syndrome, history of gestational diabetes, taking hypertensive medication or taking lipid-lowering medication.
2. Those failing exercise screening protocol, as defined within the standard operating procedure developed by the NIHR Leicester Biomedical Research Centre (e.g., chest discomfort with exertion).

Sub-study 2
Additional criteria that outline inclusion for sub-study 2:
1. Male

Sub-study 3
Additional criteria that outline inclusion for sub-study 3:
1. Safe to undertake a brain scan using magnetic resonance imaging (MRI) – the study team will determine this.
2. Able to read instructions on a TV screen without prescription glasses (contact lenses may be allowed).
3. Regularly consume Western European or Mediterranean-style foods.
4. No strict dietary requirements or food allergies (e.g., vegetarian, vegan, lactose intolerant, nut allergy).

Participant type(s)
Patient

Age group
Mixed

Lower age limit
18 Years

Upper age limit
75 Years

Sex
Both

Target number of participants
324

Key exclusion criteria

Master Exclusion Criteria

Individuals will be excluded if they meet any of the following:

1. Currently or previously (within the past 90 days before screening) participating in a weight loss intervention or group.
2. Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device. However, the following are allowed: (1) liposuction and/or abdominoplasty, if performed > 1 year before screening, (2) lap banding, if the band has been removed > 1 year before screening, (3) intragastric balloon, if the balloon has been removed > 1 year before screening or (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed > 1 year before screening.
3. Treatment with any medication for the specific purposes of weight loss within the past 90 days before screening.
4. Treatment with any GLP-1RA or DPP4 inhibitor therapies for glucose control or weight loss within the past 90 days before screening.
5. Hypersensitivity or allergy to GLP-1 agonists or their excipients.
6. Taking medication known to induce weight gain within the past 90 days before screening such as tricyclic antidepressants, atypical antipsychotics and mood stabilizers.
7. Other weight loss or gain therapy-specific contraindications as judged by the study clinician.
8. Glucocorticoid therapy (excluding topical, intraocular, intranasal, intraarticular, or inhaled preparations) within the past 90 days before screening, or have an active autoimmune abnormality that in the opinion of the trial clinician will require future treatment with systemic glucocorticoids.
9. Uncontrolled thyroid disease, defined as thyroid stimulating hormone (TSH) > 6.0 mIU/L or < 0.4 mIU/L at screening (Visit 0).
10. Those failing exercise screening protocol, as defined within the standard operating procedure developed by the NIHR Leicester Biomedical Research Centre (e.g., chest discomfort with exertion).
11. Currently taking bolus insulin or using an insulin pump.
12. HbA1c ≥ 10% at screening (Visit 0).
13. Blood pressure > 160/100 at screening (Visit 0).
14. Active or untreated malignancy or in remission for less than 3 years.
15. Current or planned pregnancy, or breastfeeding. Planned pregnancy in this instance involves women of childbearing potential (see definition in section 6.3) actively trying to become pregnant or aiming to become pregnant within the next six months.
16. Stage 3b CKD, defined as eGFR <30 ml/min/1.73m² at screening (Visit 0).
17. Any of the following: myocardial infarction, stroke, diagnosed heart failure or arrhythmogenic cardiomyopathy, atrial fibrillation, a pacemaker or implantable cardioverter defibrillator or hospitalisation for other cardiac events within the past six months.
18. Documented or self-reported liver cirrhosis.
19. Current participation in another research study with investigational medical products.
20. Serious illness with life expectancy < 1 year or other significant illness or disability which, in the opinion of the principal investigator or study clinician, precludes involvement.
21. Individuals with acute pancreatitis or a history of chronic pancreatitis.
22. Have a history of active or unstable Major Depressive Disorder (MDD) or other severe psychiatric disorder (e.g. schizophrenia, bipolar disorder) within the last 2 years. Patients with MDD or a generalized anxiety disorder whose disease state is considered stable may be considered for inclusion if they are not on excluded medications.
23. Personal or family history of Medullary Thyroid Carcinoma (MTC).
24. Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
25. Unwilling to comply with contraceptive requirements.
26. History of a serious eating disorder within the past 5 years.

27. History of substance abuse within the past 5 years.
28. Excessive alcohol intake as determined by liver function tests or the opinion of the trial clinician.

Cohort and sub-study(s) specific eligibility
Younger age cohort
Additional criteria that outline exclusion for the younger cohort:
Have a confirmed clinical diagnosis of long-COVID

Middle-to-older age cohort
Additional criteria that outline exclusion for the middle-to-older cohort:
Have a confirmed clinical diagnosis of long-COVID

Sub-study 1
Additional criteria that outline exclusion for sub-study 1:
History of bleeding disorders
Currently taking anti-coagulation therapy, high-dose statins, or growth hormones.

Sub-study 3
Additional criteria that outline exclusion for sub-study 3:
Current smoker (vaping is considered smoking in this study).

Date of first enrolment
30/09/2024

Date of final enrolment
01/10/2028

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Leicester Diabetes Centre
Leicester General Hospital NHS Trus
Gwendolen Road
Leicester
United Kingdom
LE5 4PW

Study participating centre
Diabetes Research Centre
University of Leicester
Leicester

United Kingdom
LE1 7RH

Study participating centre
Loughborough University
Epinal Way
Loughborough
United Kingdom
LE11 3TU

Sponsor information

Organisation
University of Leicester

Sponsor details
Research Governance Office, Research & Enterprise Division, University of Leicester, University Rd
Leicester
England
United Kingdom
LE1 7RH
+44 (0)116 373 6508
rgosponsor@le.ac.uk

Sponsor type
University/education

Website
https://le.ac.uk/

ROR
https://ror.org/04h699437

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer reviewed scientific journals
2. Internal report
3. Conference presentation
4. Publication on website

The study data will be available upon reasonable request from the Chief Investigator. All data sharing will use secure data transfer systems and will have all identifiable information removed (anonymisation with name, address, postcodes, date of birth and other sensitive data removed). The sharing of study data will only be for ethically approved research.

Intention to publish date
01/09/2030

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Gregory Biddle, Diabetes Research Centre, Leicester General Hospital, gjhb2@leicester.ac.uk

IPD sharing plan summary
Data sharing statement to be made available at a later date