ISRCTN47919839 https://doi.org/10.1186/ISRCTN47919839

Assessment of the effect of geroprotectors on how cells work in the human body

Submission date	**Recruitment status**	[X] Prospectively registered
06/09/2024	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
10/09/2024	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
22/06/2026	Other	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
The overall aim of this research is to accelerate research to improve the number of years spent in healthy life and promote positive ageing. People age differently and this can lead to either healthy ageing or the development of age-related conditions such as frailty and cognitive decline. We think these age-related conditions are caused by changes in how the cells within the body are working. Scientists have found that giving mice drugs to improve how the cells work led to 1) increase in the mice's lifespan and, 2) how healthy they were. These drugs are called 'geroprotectors'. However, we don't know whether they work in humans.
We want to test three different geroprotector drugs. Metformin which is a medicine for diabetes and, fisetin and spermidine which are food supplements. We have chosen these three drugs as they are safe in older adults and there is good evidence they can have a beneficial effect on the cells in the body. Metformin will be used 'off-label' in this study. This means that it has not been approved by the Medicines and Healthcare products Regulatory Agency for use as a geroprotector.

Who can participate?
Healthy older people over the age of 70 years. They must be able to travel to the research clinic and be able to read and write in English.

What does the study involve?
Participants are treated with one of three geroprotector drugs (metformin MR, fisetin or spermidine) and undergo the following tests:
Handgrip strength - Participants will be asked to squeeze a device.
Walking and balance tests - Participants will be asked to walk 4 metres and stand up and down from a chair.
Muscle ultrasound - We will scan the muscles in the participant's thigh using sound waves (similar to a pregnancy scan).
Bioelectrical impedance - We will measure the muscle and fat content in a participant's body in a way similar to a heart tracing (ECG) test.
Questionnaires - We will ask participants some questions to test their memory and thinking, and other aspects of their health.
Brainwave test - This will involve performing some simple tasks whilst a cap is placed on the

outside of a participant's head.
Blood tests - We will take a maximum of five tablespoons of blood at any time.
Fat biopsy - We will take a small sample of fat. This will be done under local anaesthetic. We will talk participants through this.
Stool tests - We will ask participants to collect samples of their stool (poo) at home to look at the different bacteria within their gut. We will give an instruction sheet to help participants do this.

What are the possible benefits and risks of participating?
Taking part in this study may not benefit participants directly. They will be contributing towards research that aims to understand how older adults respond to a 'geroprotector' drug. If this study is successful we would aim to do a bigger trial to see whether the drugs might be a treatment option for different types of patients. Ultimately, participants will be helping us to find ways to help keep the body and mind strong as we get older.
Participants will be asked to give their time to the assessments, which they might find tiring, and there is a low risk of falling when testing their walking and balance, but there will always be someone at hand to look after them. If we find new medical problems during the study we will let their GP or hospital doctor know.
Blood tests might be uncomfortable and cause a bruise. Fat biopsies could cause bleeding or infections. There is a risk of fainting during these procedures. We will take steps to make sure this is a low risk.
The drugs themselves might cause side effects which could be unpleasant. We don't expect there will be any side effects when taking the food supplements (fisetin or spermidine). This is because no side effects have been reported.
There may be gastric side effects when taking Metformin. We will reduce the risk of this by using a modified release form of the drug which is better tolerated, starting with a low dose and checking about side effects before increasing the dose. The drug can be stopped at any point if there are side effects. There is a very small risk of Metformin causing a low vitamin B12 or liver problems we will check for this after the study has finished.

Where is the study run from?
University Hospitals Birmingham NHS Foundation Trust (Queen Elizabeth Hospital Birmingham site) (UK)

When is the study starting and how long is it expected to run for?
September 2023 to June 2026

Who is funding the study?
This research project has been funded as part of a programme of work funded by the Dynamic Resilience programme funded by Wellcome Leap and Temask Trust

Who is the main contact?
Dr Daisy Wilson, d.v.wilson@bham.ac.uk

Contact information

Type(s)
Scientific

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Additional identifiers

Integrated Research Application System (IRAS)
338321

Central Portfolio Management System (CPMS)
62299

Study information

Scientific Title
REsilience PROmotion with GeRoprotectors: AssessMent of biological effect

Acronym
REPROGRAM

Study objectives
Does a 3-week course of metformin, spermidine, or fisetin reduce the number of senescent cells as measured by SA-β-GAL in adipose biopsies in healthy older volunteers?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 29/08/2024, Sessional REC, care has been transferred to Cambridge Central (Postal address: not available; +44 (0)207 104 8285, +44 (0)207 104 8089, +44 (0)207 104 8063; cambridgecentral.rec@hra.nhs.uk), ref: 24/LO/0549

Primary study design
Interventional

Study design
Non-randomized; Interventional; Design type: Treatment, Drug

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Ageing

Interventions
TRIAL DESIGN
A Phase IIa clinical trial of a 3-week intervention of one of three geroprotector drugs: metformin MR, fisetin or spermidine. This is an uncontrolled trial with no placebo arm. The outcomes are all biological measures rather than clinical. 60 participants will be recruited to start the 'geroprotector drug'. More participants may be recruited but do not meet the inclusion and exclusion criteria. The null hypothesis is that there will be no difference in our outcome measures at 3 weeks, compared to baseline. We have chosen an uncontrolled design, so all participants will be given one of the three 'geroprotector' drugs. This design has been chosen as it will demonstrate whether the 'geroprotector' drug leads to changes biologically over the 3-week period. We do not know this yet, so this is a first, pilot phase. If we can prove that the 'geroprotector' drug do make a change to senescence (cells that have stopped functioning healthily), then we would proceed to a placebo-controlled, randomised trial. The intervention period of 3 weeks has been chosen to mimic the time between a diagnosis of localised cancer and curative surgery and will attempt to determine whether the 'geroprotector' drugs could be used effectively in the prehabilitation (improving a patient's health prior to a known adverse event such as an operation or hemotherapy) process. Data analysis will compare differences within groups between pre-intervention and 3-week measures in blood and adipose (fat) tissue. We will recruit a total of 60 older people. The sample size calculation is based on measurements of SA-β-Gal (a marker of senescence in cells that have stopped functioning healthily) from a study in adults. The number of participants required at 80% power and a significance level of 0.05 to detect a mean difference of 5% in the SA-β-Gal marker is 9. To allow for drop out 10 participants of each sex will be recruited to each intervention (metformin, spermidine, or fisetin), 20 in total. We are recruiting 10 participants of each sex for each intervention as there is some evidence of sex differences with women believed to be more prone to senescence (cells that have stopped functioning healthily).

PROCEDURES
Participants will be approached through post or email, identified in our 1000 Elders research database. They will be provided with the participation information sheet and an invitation to contact the study team. They will also be given the opportunity to attend an in-person or virtual meeting to go over the rationale and details of the study and provide additional opportunities to ask questions of the research team. If they volunteer to be participants they will contact the study team. Phone Call/Email Contact 1 Once they have contacted the study team to express interest a member of the study team will contact the volunteer (either by email or phone) to discuss the inclusion and exclusion criteria. This is to ensure that we minimise the risk of ineligible volunteers attending the research facility and wasting their time. All assessments /measures will take place at the NIHR Clinical Research Facility in the Queen Elizabeth Hospital, Birmingham.

Visit 1
At the first visit written informed consent to be in the trial will be taken. Participants will also undergo a clinical assessment which we believe will take about 1 1/2 hours. This assessment is similar to previous assessments conducted by our team and has been previously well-received by participants. The assessment includes:
1. Recording diseases, medications and the answer to some questions on weight loss and physical activity
2. Questionnaires on how a participant manages with activities of daily living. For example,

whether they can cook their own dinner
3. Cognitive assessment. This is a short assessment and is a test of memory and thinking. It will take about 10 minutes and give a score out of 30.
4. Short Physical Performance Battery. This involves testing how quickly the participant walks over a short distance, how well they balance, and to see how long it takes them to stand up from a sitting position 5 times. This takes about 5 minutes to complete.
5. Grip strength. This involves testing how strong the participant's grip is using a handheld dynamometer (small piece of equipment) and is conducted whilst the participant is sat down. It will be tested twice each side and the best measurement recorded.
6. Ultrasound assessment of quadriceps. This is a painless and radiation-free way of visualising the size of the thigh muscles. It takes about 10 minutes and we have previously found this to be a well-received part of the assessment as the ultrasound operator will guide the participant through the images.
7. Bioelectrical impedance analysis. This is a measure of muscle and fat within the entire body. The participant will be asked to stand on a machine much like a weighing scale and a low electrical current will be passed through the body. This is painless. There will be some exclusion criteria for this assessment as it is not safe to conduct in individuals with pacemakers.
8. Electroencephalography. A wet net will be applied to the participant's head and waveform readings will be taken both at rest and during cognitive tasks. This will take about 15 minutes.
9. A blood test will then be taken (70 ml = 5 tablespoons) to measure both senescence and cell energy use in cells and safety bloods. The safety bloods are routine samples which will be sent to the University Hospitals Birmingham NHS Foundation Trust laboratories for analysis.
10. A food diary will be given to the participant to take home with them. They will be asked to complete a 3-day food record and bring it back to their next appointment.
11. A sterile container for stool sample collection will be given to the participant along with a protective delivery bag to either post the sample directly to the research team or hand deliver to the hospital at the earliest convenience.

Visit 2
The safety bloods will be reviewed prior to confirming with the participant the time for their second visit. If the safety bloods are ok to continue with the adipose (fat) biopsy then the participant will return to the research facility within a week of the first visit. At this visit the participant will undergo:
1. Adipose biopsy. This is a short procedure undertaken on the abdomen similar to the removal of a skin cancer. Local anaesthetic will be injected to numb the area then two small parallel cuts (2 cm in length) to the skin and the fat underlying will be made. A small wedge of fat (1 cm in depth) will be removed which will be frozen for storage. The incision will be closed with either steristrips or soluble sutures. This will all be conducted aseptically to reduce the risk of infection.
2. Drug distribution. The participant will be given a 3-week supply of the 'geroprotector' drug (4 weeks for Metformin MR).
3. Safety netting. The study team will ensure the participant knows when to contact the study team and how and who to contact in an emergency.
4. Additional blood test. The participant may be asked to provide an additional blood test. This allows the study team a bit more flexibility in how they analyse the blood samples and allows the study team to do more analyses. There is some flexibility in which visits the assessments are completed. For example, a participant may wish for a shorter Visit 1 and some of the assessments may be moved to Visit 2. However, consent and blood tests have to be performed in Visit 1 and adipose biopsy in Visit 2.

Additional Phone Call for Metformin MR
The study team will contact the participants taking Metformin MR to decide whether to increase the dose from 500 mg to 1500 mg. Any information on side effects or adverse events will be

collected. Any participants who are suffering from intolerable side effects of Metformin MR will not have the dose increased and will be excluded from the trial at this point.

Phone Call/Email Contact 2
At 10 days (+/- 3 days) after starting the 'geroprotector' drugs (or 17 days +/- 3 days for Metformin MR) the study team will contact the participants to discuss side effects and/or adverse events. These will be recorded and 'geroprotector' drugs discontinued as necessary.
Visit 3 At 28 days (fisetin/spermidine) / 35 days (Metformin MR) (+/- 3 days) the participant will attend the research clinic for a follow-up assessment. This includes:
1. A blood test will be taken (70 ml = 5 tablespoons) to measure both senescence and cell energy use in cells and, safety bloods.
2. A sterile container for stool sample collection will be given to the participant along with a protective delivery bag to either post the sample directly to the research team or hand deliver it to the hospital at the earliest convenience.
3. Adipose biopsy. This is a short procedure undertaken on the abdomen similar to the removal of a skin cancer. Local anaesthetic will be injected to numb the area then two small parallel cuts (2 cm in length) to the skin and the fat underlying will be made. A small wedge of fat (1 cm in depth) will be removed which will be frozen for storage. The incision will be closed with either steristrips or soluble sutures.
4. Adverse event reporting. The participant will be asked about side effects and any adverse events whilst taking the 'geroprotector' drugs.
5. Compliance pill count. The participants will be asked to bring in the containers the 'geroprotector' drugs were supplied in to check their compliance. They will also be asked about compliance and any problems with taking the drugs.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Metformin MR, fisetin, spermidine

Primary outcome(s)
Number of senescent cells in adipose tissue measured by the SA-β-GAL technique after 3 weeks of intervention, adjusted for the baseline number of senescent cells prior to the intervention

Key secondary outcome(s)
1. Senescent cell burden in adipose tissue as measured by transcriptomics using SenMayo analysis after 3 weeks of intervention, adjusted for baseline number of senescent cell burden prior to the intervention.
2. Epigenetic age (DNA methylation) after 3 weeks of intervention, adjusted for baseline epigenetic age prior to the intervention.
3. Immunosenescence as measured by IMM-AGE analysis after 3 weeks of intervention, adjusted for baseline IMM-AGE prior to the intervention.
4. Autophagic flux as measured by flow cytometry after 3 weeks of intervention, adjusted for autophagic flux prior to the intervention.
5. Nutrient sensing as measured by mTOR activation after 3 weeks of intervention, adjusted for baseline nutrient sensing prior to the intervention.
6. Mitochondrial function as measured by Seahorse after 3 weeks of intervention, adjusted for

baseline mitochondrial function prior to the intervention.
7. Inflammation as measured by ELISA and multiplex technology after 3 weeks of intervention, adjusted for baseline inflammation prior to the intervention.
8. Microbial composition and functional potential of stool measured using metagenomics after 3 weeks of intervention, adjusted for baseline microbial composition and functional potential prior to the intervention.

Completion date
30/06/2026

Eligibility

Key inclusion criteria
1. Age ≥70 years
2. Ability to provide informed consent
3. Able to travel to the clinic for initial and subsequent evaluations
4. Ability to understand spoken and written English

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Senior

Lower age limit
70 Years

Upper age limit
110 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Current smokers, or ex-smokers who have stopped within the last 12 months, or are using nicotine replacement products
2. History of diabetes (type 1 or 2), or untreated vitamin B12 deficiency
3. Untreated thyroid disorder
4. Active cancer - currently on treatment or palliative
5. Major surgery or trauma in the last 60 days
6. Recent infection in the last 60 days
7. Allergies or intolerance to any of the drugs to be studied
8. Any contraindication to metformin MR, as listed in the current summary of medicinal product characteristics for metformin MR

9. Any medication which significantly interacts with metformin MR, as listed in the current summary of medicinal product characteristics for metformin MR
10. Currently taking any of the following medications, which confound the effects of inflammation: tamoxifen, cyclosporine A, immunosuppressants or Anti TNF inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs).
11. Currently taking any of the following anticoagulant drugs (blood thinners): warfarin, direct oral anticoagulant drugs (DOACs), low molecular weight heparin, clopidogrel, or high-dose aspirin. Patients taking low dose ≤75 mg aspirin only may be recruited
12. Individuals at risk of bleeding complications, including those with inherited bleeding disorders (such as haemophilia), or previously unexplained haemorrhage
13. Unable or unwilling to maintain current lifestyle throughout trial such as eating habits, exercise habits, etc
14. Estimated glomerular filtration rate <45 mL/min/1.73 m2 by the Modified Diet in Renal Disease 4 (MDRD4) or Chronic Kidney Disease - EPIdemiology collaboration (CKD-EPI) equation
15. History of diarrhoeal illness within the last three months (>48 hours of Bristol stool chart grade 6 or 7)
16. Liver function tests (bilirubin, alanine aminotransferase or alkaline phosphatase) >3× upper limit of normal
17. Symptomatic chronic heart failure, diagnosed according to European Society of Cardiology guidelines (asymptomatic left ventricular systolic dysfunction will not be an exclusion criterion)
18. Life expectancy of <3 months as adjudicated by the local Investigator
19. Previous inclusion in trial investigating effects of 'geroprotector' medication
20. Allergy to local anaesthetic
21. Coeliac disease (spermidine only)
22. Contrast imaging as part of usual care during trial duration (metformin only)

Date of first enrolment
01/11/2024

Date of final enrolment
01/05/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Queen Elizabeth Hospital Birmingham
Mindelsohn Way
Edgbaston
Birmingham
England
B15 2GW

Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Charity

Funder Name
Wellcome Leap

Alternative Name(s)
Leap, Wellcome Leap Inc, Wellcome Leap, Inc.

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United States of America

Funder Name
Temask Trust

Results and Publications

Individual participant data (IPD) sharing plan

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

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?

Protocol article	version 2.0	17/06/2026	22/06/2026	Yes	No
Protocol file		23/07/2024	10/09/2024	No	No