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Can metformin prevent worsening of muscle weakness and frailty in older people who are showing early signs of frailty?

Submission date
10/04/2020

Recruitment status
No longer recruiting

Registration date
21/01/2021

Overall study status
Completed

Last Edited
23/01/2024

Condition category
Signs and Symptoms

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Frailty is a condition where the body isn't able to cope with a problem such as an injury, mild infection or other illness. Some of the first signs are losing muscle strength and slower walking. It is not yet known how best to prevent the onset of frailty. Exercise can help, and diet may also play a part. These approaches only go so far though, and new approaches including medication are also needed. Metformin is a medication that may be promising to prevent frailty by improving muscle function.
This project will test whether metformin, a medicine normally used to treat diabetes, can improve physical function in older people without diabetes at risk of developing frailty or sarcopenia (muscle weakness).

Who can participate?
People living in the North East of England aged 65 years or older who walk slowly and have low muscle strength, which means they are at risk of becoming frail, and who do not have diabetes.

What does the study involve?
Participants will be randomly allocated to one of two groups. One group will take a metformin tablet three times a day for 4 months. The other group will take a placebo (dummy) tablet three times a day for 4 months. Neither the participants nor the research team will know who is taking which tablet until the end of the study.
The researchers will measure walking speed, handgrip strength and other aspects of frailty and muscle weakness at the start and after 4 months of treatment. They will also measure activities of daily living, quality of life, muscle size, side effects of medication, and a series of blood tests to understand who might respond best to metformin to help select participants for a future large study.

What are the possible benefits and risks of participating?
Metformin is a safe medication that has been used by millions of people for over 50 years. It can cause loose bowel motions or nausea in some people, but the researchers will minimise the chances of this happening by using a low dose, and excluding anyone with recent diarrhoea. Very

rarely, metformin can cause a build up of acid in the blood (acidosis). The researchers will monitor this at the monthly visits, and they will also exclude people with poor kidney function, who may have problems expelling metformin from the body, which can increase the chances of metformin causing a build-up of acid.

Where is the study run from?
Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
April 2020 to August 2023

Who is funding the study?
NIHR Newcastle Biomedical Research Centre (UK)

Who is the main contact?
Professor Miles Witham, Miles.Witham@newcastle.ac.uk

Contact information

Type(s)
Public

Contact name
Prof Miles Witham

ORCID ID
http://orcid.org/0000-0002-1967-0990

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Additional identifiers

EudraCT/CTIS number
2020-004023-16

IRAS number
275219

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 47772, IRAS 275219

Study information

Scientific Title
Metformin to prevent progression of sarcopenia and frailty for older people – a randomised controlled proof of concept trial

Acronym
MET-PREVENT

Study objectives
4 months of metformin 500 mg three times a day will improve measures of physical performance in older people with sarcopenia and prefrailty.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 07/01/2021, North West - Liverpool Central Research Ethics Committee (**Currently being held remotely via Teleconference/ZOOM** Liverpool Women's Hospital, +44 (0)207 104 8197, +44 (0)2071048387; liverpoolcentral.rec@hra.nhs.uk), ref: 20/NW/0470

Study design
Randomized, placebo-controlled, double-blind, parallel-group trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Community

Study type(s)
Prevention

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied
Frailty and sarcopenia in older people

Interventions
Participants will be randomised 1:1 into the metformin or placebo arms using a web-based randomisation system. They will receive metformin hydrochloride 500 mg or matching placebo three times a day for 4 months. Assessments will be conducted at baseline and 4 months (all outcomes) with an additional safety assessment visit at 1 month.

Intervention Type

Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Metformin hydrochloride

Primary outcome measure
4-m walk speed at 4 months

Secondary outcome measures
1. Fried frailty score, including individual components:
1.1. Activity level assessed using self-report questionnaire at baseline and 4 months
1.2. Exhaustion assessed using self-report questionnaire at baseline and 4 months
1.3. Grip strength assessed using Jamar handgrip dynamometer at baseline and 4 months
1.4. 4-m walk speed assessed using timed walk test over 4 m at baseline and 4 months
1.5. Weight assessed using calibrated scales at baseline and 4 months
2. Transitions from pre-frail to frail, death, inability to continue in trial, or to non-frail from baseline to 4 months
3. Lower limb muscle power measured using Short Physical Performance Battery at baseline and 4 months
4. 6-min walk distance assessed at baseline and 4 months
5. Total body muscle mass measured using bioimpedance at baseline and 4 months
6. Ability to perform activities of daily living assessed using the Nottingham Extended Activities of Daily Living Scale (EADL) at baseline and 4 months
7. Health related quality of life assessed using the EQ5D and SF-36 scales at baseline and 4 months
8. Trial metrics:
8.1. Conversion from screening to randomisation assessed using study records at screening and baseline study visits
8.2. Recruitment rate assessed using study records over the 10-month recruitment period
8.3. Retention rate assessed using study records over the 4-month participation period

Overall study start date
01/04/2020

Completion date
31/08/2023

Eligibility

Key inclusion criteria
1. Aged 65 years or over
2. Low maximum handgrip strength (<16 kg for women, <27 kg for men)
3. Walk speed <0.8 m/s on 4-m walk test

Participant type(s)
Patient

Age group
Senior

Lower age limit
65 Years

Sex
Both

Target number of participants
80

Total final enrolment
72

Key exclusion criteria
1. Diabetes mellitus (type 1 or type 2)
2. eGFR <45 ml/min/1.73 m2 by MDRD4 or CKD-EPI equation
3. History of diarrhoeal illness within the last 3 months (>48 h of Bristol stool chart grade 6 or 7)
4. Alcohol intake >21 units/week (women) or >35 units/week (men)
5. Symptomatic chronic heart failure, diagnosed according to European Society of Cardiology guidelines (asymptomatic left ventricular systolic dysfunction will not be an exclusion criterion)
6. Liver function tests (bilirubin, alanine aminotransferase or alkaline phosphatase) >3x upper limit of normal
7. Oral steroid dose >7.5 mg prednisolone equivalent per day
8. Unable to mobilise without human assistance
9. Life expectancy of <3 months as adjudicated by the local investigator
10. Unable to give written informed consent
11. Previous intolerance of metformin or taking metformin for another condition
12. Currently participating in, or participated within 30 days, another intervention study (observational studies and registries are permitted)

Date of first enrolment
01/04/2021

Date of final enrolment
30/09/2022

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Campus for Ageing and Vitality
Biomedical Research Building
Newcastle University

Newcastle upon Tyne
United Kingdom
NE4 5PL

Study participating centre
Queen Elizabeth Hospital
Queen Elizabeth Ave
Gateshead
United Kingdom
NE9 6SX

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

Sponsor details
Newcastle Joint Research Office
Regent Point
Regent Road
Newcastle upon Tyne
England
United Kingdom
NE3 3HD
+44 (0)191 282 4461
sean.scott@nhs.net

Sponsor type
Hospital/treatment centre

Website
http://www.newcastle-hospitals.org.uk/

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Research organisation

Funder Name

NIHR Newcastle Biomedical Research Centre

Alternative Name(s)
Newcastle Biomedical Research Centre, Newcastle NIHR Biomedical Research Centre

Funding Body Type
Private sector organisation

Funding Body Subtype
Research institutes and centers

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Main trial results will be published within 18 months of the end of the trial, and results will be presented as a conference abstract within 12 months of the end of the trial. Results will be fed back to participants via a newsletter and an in-person end-of-study event.

Intention to publish date
31/01/2024

Individual participant data (IPD) sharing plan
The datasets generated during the current study will be available upon request from the Chief Investigator (Professor Miles Witham, Miles.Witham@newcastle.ac.uk). Deidentified, individual participant-level data will be available to bona-fide academic research teams from 12 months after the end of the trial, subject to submission of an outline of the purpose for which it will be used, and subject to approval by a Data Access Committee process hosted by the trial funder (NIHR Newcastle Biomedical Research Centre). Consent will be obtained from participants for this data sharing.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Protocol article		18/07/2022	18/08/2023	Yes	No
Basic results		19/12/2023	19/12/2023	No	No
Plain English results		23/01/2024	23/01/2024	No	Yes