ISRCTN87213295 https://doi.org/10.1186/ISRCTN87213295

Fludrocortisone and midodrine for the treatment of orthostatic hypotension

Submission date
10/05/2021

Recruitment status
No longer recruiting

Registration date
23/07/2021

Overall study status
Completed

Last Edited
30/09/2025

Condition category
Circulatory System

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

Plain English summary of protocol

Background and study aims
Orthostatic hypotension (OH) is a drop in blood pressure (BP) on standing up from a sitting or lying position. The drop in BP can lead to unpleasant symptoms such as dizziness, fainting, and falls. It is a common problem, affecting one in five older people and one in three people with Parkinson's disease.

Doctors usually treat OH without tablets and medicines, instead giving patients advice on drinking more water, wearing compression stockings and performing muscle tensing exercises (known as non-drug therapies). When these non-drug therapies don't help, patients are offered medication. The two most commonly used drugs for OH are fludrocortisone and midodrine. However, there has been very little research on whether these treatments work. So nobody really knows what the ideal treatment is
for OH.

To find out what the best treatment is, the CONFORM-OH clinical trial is comparing fludrocortisone and midodrine to non-drug therapies (known as usual care). People with OH have told us that symptoms are the most important outcome to them, so any change in symptoms in all three groups after six months of treatment will be measured. The effects on quality of life, daily activities, falls, BP, side effects, and costs to the NHS for a total of 12 months will also be looked at.

A novel feature of this trial, is that after the 200th participant a provisional review of the effectiveness of the treatments will be performed. This will allow one of the study treatments to be stopped if it is ineffective so the focus can be on the one with the most potential. A six-month pilot of the study (a small-scale version of the study) to identify and resolve any problems before continuing with the main trial will also be run.

Who can participate?
Adults with OH in 20 different hospitals in the UK, where OH persists after simple treatments, such as standing up slowly, avoiding dehydration, and reducing medications that cause OH have been tried for 4 weeks.

What does the study involve?
There is a baseline visit where discussions about the study take place and consent is obtained if the patient wishes to take part. At this visit, some baseline assessments will be performed such as lying and standing blood pressure. Patients will also be given some questionnaires to complete. It is at this visit patients will be allocated to one of the treatment arms. Participants will be allocated to one of three groups, to receive usual care, fludrocortisone or midodrine, with an equal chance of being in each group (like tossing a coin). The study medication will be taken for 12 months.

There are further study visits at 3, 6, and 12 months. At these visits lying and standing blood pressure will be taken and there will be more questionnaires to complete. For the participants' convenience and to reduce burden, the study visits will be arranged in line with standard care clinic appointments as much a possible and can be conducted in the clinic or in their own home, based on their preference. Each participant will also be given a paper falls diary to complete at home if they experience any falls.

What are the possible benefits and risks of participating?
There are minimal risks in this study as all of these treatments are currently used in the NHS.

Participants will receive one of three routine treatments for OH, however, all medical treatments carry some risk of side effects. Although Fludrocortisone is used routinely in the NHS to treat OH, it does not have a specific license to treat OH, this means that there currently isn't enough information to show whether fludrocortisone works well enough, or is safe enough to be used to treat OH. Midodrine is currently licensed to treat severe OH in standard care.

Blood pressure and side effects will be monitored throughout the study.

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

When is the study starting and how long is it expected to run for?
From November 2019 to December 2024

Who is funding the study?
The National Institute for Health Research (UK)

Who is the main contact?
Emma Clark
conform.oh@newcastle.ac.uk

Contact information

Type(s)
Public, Scientific

Contact name
Miss Emma Clark

ORCID ID
https://orcid.org/0000-0003-0065-1463

Contact details
Trial Manager
Newcastle Clinical Trials Unit
Newcastle University
1-4 Claremont Terrace
Newcastle upon Tyne
United Kingdom
NE2 4AE
+44 (0)191 208 2519
conform.oh@newcastle.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2020-000794-25

Integrated Research Application System (IRAS)
277408

Central Portfolio Management System (CPMS)
49254

Protocol serial number
Sponsor R&D Number 09389

Study information

Scientific Title
CONtrol, Fludrocortisone OR Midodrine for the treatment of Orthostatic Hypotension (CONFORM-OH): a randomised controlled trial

Acronym
CONFORM-OH

Study objectives
To determine whether the treatment strategies of conservative management plus fludrocortisone and conservative management plus midodrine improve symptoms of orthostatic hypotension compared to conservative management alone.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 14/06/2021, North East – Newcastle and North Tyneside 1 (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 (0)207 104 8285; newcastlenorthtyneside1.rec@hra.nhs.uk), ref: 21/NE/0083

Primary study design
Interventional

Study design
Multicentre open-label parallel-group pragmatic randomized multi-arm multi-stage prospective superiority trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Orthostatic hypotension

Interventions
The study will compare conservative management, conservative management plus fludrocortisone, and conservative management plus midodrine in a randomised parallel trial, with a 10-month internal pilot.

Patients who receive a clinical diagnosis of symptomatic orthostatic hypotension (OH) refractory to a minimum of 4 weeks of lifestyle modification will be randomised. Participants will be randomised on a 1:1:1 ratio to one of three interventions for 12 months; conservative management only (non-pharmacologic treatments), conservative management plus fludrocortisone, or conservative management plus midodrine. Randomisations will be carried out by a delegated and trained member of the research team at each site using the Sealed Envelope system (a central, secure, 24-hour web-based randomisation system). This is an open label, unblinded trial so study participants, clinicians and the trial management team will all be aware of the treatment allocation.

If randomised to the fludrocortisone or midodrine arm, IMP will be started as soon as possible after randomisation. IMP will be provided, open-label, by the site's local clinical teams according to their usual prescribing practices.

For the dosage schedule, the usual local clinical practice will be followed at sites. A typical starting dose of fludrocortisone will be 100 micrograms, once daily orally. However, at the discretion of the treating clinician starting dose of 50 micrograms is acceptable for frailer patients. The typical starting dose for Midodrine will be 2.5 mg three times a day orally, but lower doses and frequencies are acceptable if clinically indicated. Sites are encouraged to titrate doses upward to the highest tolerated, clinically effective dose, ideally within three months, before collection of the first study outcome data.

During the course of the study, the clinical team may consider crossing over of treatment arms, if they judge clinically that a treatment is not working. The same consideration may be made for combination treatments. While the trial does not seek to dictate clinical decisions, clinical teams are asked to allow sufficient time (at least four weeks) on maximum tolerated dose, and ideally until the primary outcome is assessed at six months, before considering changing allocated treatment.

Conservative management is standard first-line care and forms the control arm of this trial. The specific conduct of conservative management will vary between sites; it may consist of education about the condition, trigger avoidance, safe standing, physical counter-manoeuvres, fluid and salt intake, and the use of compression hosiery. Conservative management will begin following diagnosis as is usual clinical practice.

The effectiveness of the interventions is assessed by the change in the Orthostatic Hypotension questionnaire at 6 months. Quality of life, activities of daily living, number of falls, postural blood pressure drop, costs to the participants, NHS and social services, and side effects over the 12 months will also be assessed. Outcomes are followed up at 3, 6, and 12 month timepoints.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
fludrocortisone, midodrine

Primary outcome(s)
Symptoms of orthostatic hypotension measured using change in the Orthostatic Hypotension Questionnaire (OHQ) score at baseline and 6 months.

Key secondary outcome(s)
1. Health-related quality of life measured using the EuroQol 5-dimension 5-level (EQ-5D-5L) questionnaire at baseline, 3, 6, and 12 months
2. Activities of daily living (ADLs) measured using the Nottingham Extended ADL scale at baseline, 3, 6, and 12 months
3. Falls (number of falls, number of fallers/non-fallers, fall rate per person-year, time to first fall, fall-related injuries, and number of syncopal events) measured using participant diary at baseline, 3, 6, and 12 months
4. Standing blood pressure and postural blood pressure drop measured using sphygmomanometer at baseline, 3, 6, and 12 months
5. Quality-adjusted life years (QALYs) estimated from responses to the EQ-5D-5L questionnaire at baseline, 3, 6, and 12 months
6. Costs to the NHS, personal social services, and patients measured using ... at 12 months
7. Cost-effectiveness of each treatment strategy modelled from a patient and NHS and personal social services perspective measured in terms of the incremental costs per QALY gained at 12 months
8. Side effects and the safety data associated with each treatment strategy measured using participant records at baseline, 3, 6, and 12 months

Completion date
31/01/2024

Eligibility

Key inclusion criteria
Current inclusion criteria as of 12/02/2024:

1. Aged aged 18 years and over
2. Clinical diagnosis of symptomatic orthostatic hypotension (OH) which is either:
i.Clinically significant where you would wish to start treatment quickly without a trial of lifestyle modification OR
ii.Refractory to an adequate period of lifestyle modification (to be judged clinically)

3. A drop in systolic blood pressure of ≥20 mmHg and/or a drop in diastolic blood pressure of ≥10 mmHg, within three minutes of standing upright from a supine position (or on tilt-testing) which has been obtained in the preceding eight weeks
4. A score of f ≥2 on the Orthostatic Hypotension Questionnaire (OHQ)
5. Willing and able to provide informed consent prior to any trial procedures taking place

_____

Previous inclusion criteria:

1. Aged ≥18 years
2. Clinical diagnosis of symptomatic orthostatic hypotension (OH) refractory to a minimum of 4 weeks of lifestyle modification
3. Drop in systolic blood pressure of ≥20 mmHg and/or a drop in diastolic blood pressure of ≥10 mmHg, within 3 min of standing upright from a supine position which has been obtained in the preceding 8 weeks
4. Orthostatic Hypotension Questionnaire (OHQ) score of ≥2
5. Willing and able to provide informed consent prior to any trial procedures taking place

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
13

Key exclusion criteria
1. Orthostatic hypotension (OH) secondary to acute or reversible causes such as haemorrhage or sepsis
2. Use of fludrocortisone or midodrine within the last six months
3. Terminal illness or life expectancy <12 months
4. Unable to stand upright without assistance
5. Supine hypertension (where the risks of treatment outweigh the benefits) at baseline
6. Known allergy to study medication
7. Known contra-indication to fludrocortisone or midodrine which outweighs the potential clinical benefit, for example, if in usual clinical care the clinician and participant feel the risks outweigh the benefits, they would be excluded
8. Current or planned pregnancy or breast feeding during the trial period. If randomised to either pharmacological arm the participant, if of child-bearing potential, must have a negative urine beta-human chorionic gonadotropin (β-hCG) pregnancy test and are required to use a

highly effective contraceptive method during the trial.
9. Inability to communicate in English
10. Inability to comply with the study procedures as specified in the schedule of events
12. Currently taking part in another clinical trial that would interfere with the outcomes of CONFORM-OH

Date of first enrolment
01/07/2021

Date of final enrolment
31/08/2022

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Freeman Road
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Gateshead Health NHS Foundation Trust
Queen Elizabeth Hospital
Sheriff Hill
Gateshead
United Kingdom
NE9 6SX

Study participating centre
Norfolk and Norwich University Hospitals NHS Foundation Trust
Colney Lane
Colney
Norwich
United Kingdom
NR4 7UY

Study participating centre
Walsall Healthcare NHS Trust
Manor Hospital
Moat Road
Walsall
United Kingdom
WS2 9PS

Study participating centre
Dumfries & Galloway Royal Infirmary
Cargenbridge
Dumfries
Dumfries and Galloway
United Kingdom
DG2 8RX

Study participating centre
Royal United Hospitals Bath NHS Foundation Trust
Combe Park
Bath
United Kingdom
BA1 3NG

Study participating centre
Royal Devon University Healthcare NHS Foundation Trust
Royal Devon University NHS Ft
Barrack Road
Exeter
United Kingdom
EX2 5DW

Study participating centre
Lewisham and Greenwich NHS Trust
University Hospital Lewisham
Lewisham High Street
London
United Kingdom
SE13 6LH

Study participating centre
Northern Care Alliance NHS Foundation Trust
Salford Royal
Stott Lane
Salford
United Kingdom
M6 8HD

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Government

Funder Name
National Institute for Health 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

Individual participant data (IPD) sharing plan
NCTU recognises that there may be significant value to patients and the wider clinical community in sharing data collected during clinical trials and clinical studies. NCTU is committed

to enabling this to happen when appropriate.
Unless specific restrictions apply, all information sheets and consent forms for new studies being run in collaboration with NCTU will include a statement confirming our intention to share anonymised or pseudonymised data with the scientific community following the end of the trial /study. The following statement will appear in trial protocols:
"Data from this trial/study may be available to the scientific community subject to appropriate ethical approval. Requests for data should be directed to the lead author/Chief Investigator and Clinical Trials Unit."
In certain circumstances data sharing may be planned to occur during the trial, and processes for this should be included in the protocol.

Principles for data sharing
The processing of requests for data sharing is iterative and will follow these guiding principles:
1. Whether all required/expected publication outputs from the primary research have been completed. No data will be released if this will compromise an ongoing trial.
2. That the request for data sharing comes from a reputable source (such as a dedicated research institute or established clinical researcher) and includes individuals suitably qualified to undertake the further analyses described in the request for data.
3. Whether the proposed research that the data will inform is scientifically valid and acceptable.
4. Whether there are any contractual, legal or ethical restrictions on the data being shared including compliance with the General Data Protection Regulations; when applicable an appropriate data sharing agreement will be required between the parties, and ethical approval may need to be sought.
5. Whether there are sufficient funds available to undertake the preparation work to anonymise /pseudonymise the data prior to release if this has not previously been undertaken; where required, resources to undertake the work will be borne by the person/group requesting the data.

Who makes the decision?
During the trial any requests for data sharing must be submitted to the lead author/Chief Investigator who will consider requests in conjunction with the Trial Management Group including senior members of the Clinical Trials Unit, Sponsor, and oversight committees. After the trial has completed, approaches should be made to the Clinical Trials Unit which will consider requests in conjunction with the Chief Investigator, senior members of the Clinical Trials Unit, and Sponsor.

All publications will contain the following data sharing statement:
'A de-identified dataset will be prepared and stored by Newcastle University. Requests for data sharing will be subject to request which should provide a clear purpose, analysis plan, how the results will be disseminated, and who the authors will be. Data transfer will be subject to completion of a Data Sharing Agreement between Newcastle University and the end users.'

IPD sharing plan summary
Available on request, Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		26/09/2025	30/09/2025	Yes	No
Basic results		04/07/2024	08/07/2024	No	No
HRA research summary			28/06/2023	No	No
Other files	Health Economics Analysis Plan version 1.0	31/07/2023	07/03/2024	No	No

Protocol file	version 6.0	21/12/2022	12/02/2024	No	No
Statistical Analysis Plan	version 1.0	15/06/2023	12/02/2024	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes