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Synopsis

Control, Fludrocortisone or Midodrine for the treatment of Orthostatic Hypotension: CONFORM-OH pilot RCT and economic evaluation

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Abstract

Background: Orthostatic hypotension is a significant drop in blood pressure upon standing upright. It is very common and can result in symptoms such as postural dizziness, fainting and falls. Within the United Kingdom National Health Service, there are three principal treatments: non-drug therapies, and two medications – fludrocortisone or midodrine. Despite this we do not know which treatments are the most effective, nor whether they are cost-effective.

Objective: Evaluate the feasibility of a randomised trial to evaluate the clinical and cost-effectiveness of fludrocortisone and midodrine in comparison to non-drug therapies for the treatment of orthostatic hypotension.

Design: A 10-month pilot of a pragmatic, open-label, randomised, prospective, superiority, multiarm, multistage clinical trial. The pilot evaluated recruitment, attrition, crossover and quality of outcomes.

Setting: Falls and Syncope, Movement Disorder, Geriatrics, and Cardiology clinics in United Kingdom National Health Service secondary care.

Participants: Adults with symptomatic orthostatic hypotension.

Interventions: Control: Non-drug therapies (conservative management). Interventions: Conservative management plus fludrocortisone (50–400 mcg daily) or conservative management plus midodrine (5–30 mg daily).

Main outcome measures: Recruitment: Target was 40–64 participants from 14 sites. Attrition target: ≤ 15% participants withdraw before the primary end point. Crossover: To determine the rates of crossover between intervention arms. Outcome data: Assess the quality and completeness of outcomes. Other important outcomes included feedback via questionnaire and interview from sites and participants.

Results: Two hundred and eighty-two patients were screened for eligibility during the pilot; of these, 13 were recruited from 4 of 9 open sites. Current or recent use of one of the study medications accounted for 120 (52%) exclusions due to ineligibility. At the primary end point of 6 months, 10 of the 13 participants (77%) remained in the

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study. Of those, completion rates for primary and secondary outcomes were 100%, except for the falls diaries, which was 60%.
Feedback from sites revealed that redeployment of clinical and research staff due to COVID-19 negatively impacted on site opening and screening for eligible participants. Adapting the protocol to make it more flexible for remote clinics and more pragmatic for clinical use did not improve recruitment.
Limitations: The sample size is too small to provide a reliable estimate of attrition and crossover rates for future studies.
Conclusions: This study was not feasible in its current design. COVID-19 had an impact on staffing and site opening, while the exclusion criteria limited recruitment.
Future work: To answer the research question, novel trial designs are needed.
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Synopsis

Research papers synthesised in this synopsis

Mossop H, Al-Ashmori S, Sotire T, Clark E, Watson G, Witham MD, *et al*. Control, Fludrocortisone or Midodrine for the treatment of Orthostatic Hypotension (CONFORM-OH): results from an internal pilot randomised controlled trial. *Pilot Feasibility Stud* 2025;**11**:118. https://doi.org/10.1186/s40814-025-01704-7

The full protocol, statistical analysis plan and health economic analysis plan are available on the ISRCTN website: ISRCTN87213295.

Rationale

In 2018, the UK National Institute for Health and Care Research Health Technology Assessment (NIHR HTA) Programme opened a call for commissioned research on 'Management of orthostatic hypotension (HTA 18/32)'.

Background

Orthostatic hypotension (OH) is a common and disabling condition, characterised by a significant reduction in blood pressure (BP) on standing upright.[1] It is particularly prevalent in older populations and in those with chronic disease, affecting up to one in five community-dwelling older people, one in four with diabetes and one in three with Parkinson's disease (PD).[2–4] In the USA, the presence of OH in people with PD is known to increase overall healthcare-related costs 2.5-fold compared to those who have PD without OH.[5]

The reduction in BP during standing leads to a wide variety of symptoms including dizziness, headache, nausea, fatigue and visual disturbance; at its most severe it can result in falls and syncope.[6,7] People with OH have a reduced quality of life due to the difficulties in performing even simple tasks which involve standing.[8] There are also longer-term sequelae, as OH is associated with an increased risk of stroke, cognitive impairment and all-cause mortality.[9,10]

Despite the high prevalence of OH, there is very little good quality evidence to support its management.[11] The UK's National Institute for Health and Care Excellence (NICE) provides evidence summaries for fludrocortisone and midodrine to treat OH, but notes that long-term efficacy and safety are unclear.[12,13] NICE also comments that these studies are limited by their use of disease-centred outcomes (i.e. BP) rather than patient-centred outcomes, such as symptoms and quality of life.

Following conservative measures, including physical counter manoeuvres and fluid and salt loading, the European Society of Cardiology recommends the use of midodrine or fludrocortisone for OH but notes that the quality of evidence is based on expert opinion and/or small studies and that further research is needed.[14] Similarly, systematic reviews and meta-analyses consistently describe existing evidence as poor quality, calling for more rigorous evaluation to guide clinical practice.[14–18] Both agents have side effects, but as their relative effectiveness is unclear, it is unknown whether the benefits outweigh their harms.

The medications to treat OH are inexpensive but the cost–consequences of successful treatment or management of side effects are not known. No high-quality economic evaluations comparing these interventions, with each other or against non-pharmacological therapies, have been identified. Therefore, the lack of evidence on the relative cost-effectiveness of fludrocortisone and midodrine means that there is insufficient evidence about which of these therapies represents a good use of scarce healthcare resources.

Objectives

The objectives of this internal pilot were to determine the feasibility of completing a full trial by evaluating

recruitment, attrition, crossover, and quality and completion of outcomes.

Methods

Design

CONFORM-OH was designed as a pragmatic, multiarm, multistage, parallel group, prospective, randomised, open label, superiority trial, with a 10-month internal pilot. Participants were randomised in a 1 : 1 : 1 ratio to conservative management, conservative management plus fludrocortisone or conservative management plus midodrine. The intervention and follow-up were for 12 months.

The internal pilot was incorporated to address uncertainties in the study design and aimed to assess the feasibility of reaching the recruitment target, evaluate the rate of attrition and assess the crossover between arms. The aim was to open 20 sites in a staged approach, with 14 sites planned to be open by the end of the 10-month pilot. The estimated rate of randomisation was 0.8 participants per site per month with a target of 64 participants at 10 months. A traffic light system was in place where recruitment would be considered unfeasible if fewer than 40 participants had been recruited after 10 months.

Participants and setting

Eligible participants were adults with a clinical diagnosis of symptomatic OH, with a score of ≥ 2 on the OH questionnaire, and a drop in systolic BP of ≥ 20 mmHg and/or a drop in diastolic BP of ≥ 10 mmHg within 3 minutes of standing upright. Patients were excluded if OH was secondary to acute or reversible causes, if fludrocortisone or midodrine had been used within the last 6 months, or where there was a known allergy or contraindication to one or both of the study medications. A full list of inclusion and exclusion criteria are given in the protocol.

Participants were recruited from secondary care sites, which included falls and syncope clinics, movement disorders services, geriatrics clinics and cardiology clinics across the UK NHS.

Interventions

Control

Non-pharmacological therapies (or conservative management) included trigger avoidance, physical countermanoeuvres, fluid and salt intake, compression hosiery and 'culprit' medication review.

Fludrocortisone

A once-daily oral tablet with dosage ranging from 50 mcg per day to a maximum of 400 mcg per day.

Midodrine

An oral medication with doses ranging from 2.5 mg twice per day, increasing to a maximum tolerated dose, not exceeding 10 mg three times per day.

Outcome measures

Feasibility outcomes included the total number recruited, the average recruitment rate per site per month, the proportion of participants withdrawing from the trial, the proportion of participants crossing over between trial treatments, and the proportion of outcome assessments completed out of those expected.

The primary effectiveness outcome measure was the change in OH-related symptoms from baseline to 6 months measured using the Orthostatic Hypotension Questionnaire (OHQ). Secondary outcomes included change in activities of daily living, assessed via the Nottingham Extended Activities of Daily Living (NEADL) questionnaire, nadir standing BP, postural BP drop, falls and syncope rates, and side effects and safety.

Data collection

Questionnaires were completed by participants either during research visits, remotely over the telephone or returned via post.

Blood pressure was measured during either a research, usual clinic appointment or home visit. Where it was not possible for the participant to attend, a recent measurement from the participant's medical records was permissible. As a contingency measure, participants were able to perform their own postural BP assessment at home after being provided with a study BP monitor and instructions.[19]

Falls data were collected via participant diaries. Adverse events were identified through participant self-report or during questioning during research visits.

If participants withdrew from the study, consent was requested to use routinely collected clinical data.

Statistical analysis

All data were reported according to randomised treatment group, following the intention-to-treat principle, with the exception of safety data which were reported according to treatment strategy received to account for crossovers between intervention groups.

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Due to the small number of participants recruited, all data were summarised descriptively, and no hypothesis testing was performed. Continuous outcomes were reported using the mean and standard deviation (SD) and/or the median and range (minimum and maximum values). Categorical outcomes were reported as frequencies and percentages. The OHQ and NEADL questionnaires were scored according to published scoring methods.[6,20] Change from baseline to each follow-up time point was calculated as the follow-up score minus the baseline score.

Full details, including the analysis methods which would have been used had the trial continued past the internal pilot stage, can be found on the on the ISRCTN website: ISRCTN 87213295.

Health economics

The health economic analysis plan can be found on the on the ISRCTN website: ISRCTN 87213295. If the trial had progressed beyond the pilot, the primary objective of this analysis would have been to evaluate the cost-effectiveness of the interventions: conservative management plus fludrocortisone and conservative management plus midodrine relative to the control, conservative management, for the treatment of OH.

Due to the limited number of recruited participants, health service utilisation and EuroQol-5 Dimensions, five-level version (EQ-5D-5L) responses were summarised using descriptive statistics. A formal economic evaluation was not undertaken. Analogous to the statistical analysis methodology outlined above, continuous outcomes are presented using the mean and SD and/or the median and range (minimum and maximum values). Categorical outcomes are conveyed as frequencies and percentages. For the EQ-5D-5L, we provide responses following the descriptive framework and EuroQol-5 Dimensions visual analogue scale (EQ-5D-VAS).

Results

By March 2020, 41 sites had expressed an interest to recruit. Of these, 20 did not return site feasibility questionnaires and were excluded. The process of gaining sponsorship and ethical permission took 9 months. The first site opened in December 2021 with a further eight sites open by May 2022. Twelve sites were in the process of being set up when the pilot phase ended. Specific sites and their screening and recruitment figures can be found in *Table 1*.

Between the 3 December 2021 and 31 August 2022, 13 participants were randomised from 4 of the 9 recruiting centres.

Progress against the internal pilot progression criteria was evaluated by the Trial Steering Committee (TSC) on 30 August 2022. Nine sites had been open to recruitment for a total of 52 site months and 13 participants had been randomised. The average accrual rate was 0.25 participants per site per month, which fell well below the progression criteria target. On the recommendation of the TSC the

TABLE 1 Recruitment and screening data by site

Site	Months open	Number screened	Number eligible	% eligible (of screened)	Number recruited	% recruited (of eligible)
Newcastle	9	52	11	21	5	45
Walsall	7	79	21	27	6	29
Norfolk and Norwich	7	26	6	23	1	17
Dumfries and Galloway	7	10	4	40	1	25
Lewisham and Greenwich	6	16	3	19	0	0
Gateshead	5	3	0	0	0	0
Devon and Exeter	4	3	1	33	0	0
Bath	4	87	3	3	0	0
Salford	3	6	0	0	0	0
Total	**52**	**282**	**49**	**17.4**	**13**	**26.5**

trial closed to recruitment on 31 August 2022, 1 month earlier than the original planned 10-month internal pilot phase. All participants who had been recruited continued in the trial as planned.

In total, 282 patients were screened for eligibility. Forty-nine patients (17%) were found to be eligible and of those, 13 (27%) were randomised. Reasons for ineligibility and eligible patients not taking part in the trial are tabulated in *Table 2*. The main reason for ineligibility was due to use of fludrocortisone or midodrine within the last 6 months (120 of 233 ineligible patients; 52%). A contraindication to fludrocortisone or midodrine also led to the exclusion of 25 (11%) patients; predominantly contraindications were to midodrine.

Thirty-six of the 49 (73%) eligible patients did not take part in the trial. Thirty (83%) declined participation; the burden of completing trial assessments was the most common reason given (10 of 30; 33%).

TABLE 2 Screening data

Screened	*N* = 282
Eligibility status	
Eligible	49 (17%)
Ineligible	233 (83%)
Reasons for ineligibility	*N* = 233
Use of fludrocortisone or midodrine within the last 6 months	120 (52%)
Drug used	
Fludrocortisone	45 (38%)
Midodrine	64 (53%)
Both	10 (8%)
Unknown	1 (1%)
Current or previous use	
Current	116 (97%)
Previous	3 (3%)
Not available	1 (1%)
A known contraindication to fludrocortisone or midodrine which outweighs the potential clinical benefit	25 (11%)
Drug contraindicated	
Midodrine	19 (76%)
Both	2 (8%)
Unknown	4 (16%)
Inability to comply with the study procedures as specified in the schedule of events	21 (9%)
Supine hypertension (where the risks of treatment outweigh the benefits) at baseline	20 (9%)
Other: A score of < 2 on the OHQ	12 (5%)
Other: Too frail/pre-existing conditions	7 (3%)
Other: No BP drop as per inclusion criteria	6 (3%)
OH secondary to acute or reversible causes	5 (2%)
Other: Unable to provide informed consent	2 (1%)
Other: Already started on other medication/ did not want to start new	2 (1%)

continued

TABLE 2 Screening data (*continued*)

Screened	*N* = 282
Other: Unable to wait 4 weeks of lifestyle modification	2 (1%)
Terminal illness or life expectancy < 12 months	1 (< 0.5%)
Inability to communicate in English	1 (< 0.5%)
Other: Did not have OH on examination	1 (< 0.5%)
Other: Unknown reason	3 (1%)
Eligibility status unknown	5 (2%)
Reasons for eligible patients not participating	*N* = 36
Participant declined	30 (83%)
I would find it difficult to participate (e.g. due to burden of assessments/questionnaires)	10 (33%)
No reason given	8 (27%)
I do not want to change my treatment plan	5 (17%)
I see no benefit in the study to me	2 (7%)
I do not want to be randomised to usual care	2 (7%)
Other: Did not want to be randomised into either IMP	2 (7%)
I am too busy	1 (3%)
Participant relocated/unable to contact after screening	3 (8%)
Patient not approached by doctor	3 (8%)

A discussion of the barriers to recruitment, assessment of the feasibility components and lessons learnt from the internal pilot are summarised in *Table 3*.

Of the 13 participants randomised, 3 were allocated to control, 4 were allocated to fludrocortisone and 6 were allocated to midodrine (*Figure 1*).

Of the three participants allocated to the control arm, two (67%) withdrew from the trial, one prior to the 3-month visit and one prior to the 6-month visit; one further participant died prior to the 3-month visit. Of the four participants allocated to the fludrocortisone arm, one (25%) participant decided not to take their allocated study medication but continued to provide follow-up data. Of the six participants allocated to the midodrine arm, two (33%) participants discontinued their allocated treatment, one participant crossed over to fludrocortisone at the 3-month visit due to side effects of midodrine and one participant stopped taking midodrine at the 6-month visit as their symptoms had improved. One participant allocated to the midodrine arm was lost to follow-up prior to the 12-month follow-up visit. At the 6-month primary outcome time point, data were available for 10 (77%) participants; 0 (0%) allocated to control, 4 (100%) fludrocortisone and 6 (100%) midodrine.

The non-drug therapies, which were used are listed in *Appendix 1*, *Table 5*, summarised as the number of sites using each therapy at least once, and the number of participants advised to use each therapy. Advice about hydration was the most common therapy, followed by trigger avoidance and physical counter-manoeuvres.

Availability of outcome data is summarised in *Table 4*. The OHQ and NEADL questionnaire were available for all participants who remained in follow-up at each time point. BP measurements were also available for all participants who remained in follow-up; however, no routine measurements were collected from routine sources for participants who withdrew from trial follow-up. Falls diaries were completed by seven (64% of those remaining in the trial), six (60%) and five (56%) participants at the 3-, 6-, and 12-month visits, respectively.

The primary and secondary outcome data are provided in *Appendix 1*, *Table 6* and *Figure 2*.

TABLE 3 Summary of learning from feasibility components

Feasibility issues	Key findings and learning
Permissions	Ethical permissions were delayed due to prioritisation of COVID-19 studies.
Site opening	Clinical and research staff redeployed during and after COVID-19.
Eligible patient population	The biggest barrier to recruitment was the exclusion criteria, predominantly by excluding those already taking one of the trial interventions. Potential solutions include having a washout period before entering the trial, although this may not be acceptable to patients and clinicians and prior experience of treatment may introduce bias.
Acceptance rate	One third of eligible participants declined due to the burden of assessments. Given the level of frailty and multiple long-term conditions in this population, this may be expected. Feedback from trial participants was that the number of assessments was not burdensome.
Intervention crossover	Given the low numbers of participants, the estimate is unlikely to be of a value. Participants and clinicians reported reluctance to be randomised to the conservative arm; had the trial continued, this may have led to increased crossover from the control arm to one of the intervention arms.
Retention	Retention was 100% at the primary time point of 6 months for the intervention arms but was 0 of 3 for the control arm. Retention remained good (90%) for the intervention arms at 12 months. As described above, the control arm appears to have been a barrier to recruitment and retention, although numbers in all arms were small to make definitive conclusions.
Availability of outcome measures	With the exception of the falls diaries, completion rate of the outcomes was excellent. Of those remaining in the trial, the primary outcome was available for all participants. Of secondary outcomes, with the exception of falls diaries, these were all available for all participants at all time points. Return rates for falls diaries are known to be poor in falls studies. Strategies such as telephone and text reminders may help. One participant stated they would have preferred an online falls diary. In one participant who did not return their falls diary, a review of their medical records identified an injurious fall. Reviewing medical records will likely improve identification of injurious falls rather than relying on self-report.

Full details of all primary and secondary outcome data and safety data are reported in *Appendix 1*, *Figure 2* and *Table 6* and *Report Supplementary Material 1* and in https://doi.org/10.1186/s40814-025-01704-7.

Health economics

Report Supplementary Material 1, *Tables 1–22* present summary health and social services utilisation data. Data reported by randomised arm and overall, for responses at baseline, 3- , 6- and 12-month follow-up. No direct comparisons are made between the trial arms due to the limited data available. A small subset of participants exhibits more appointments with general practitioners than the rest of the trial's participants, causing a right skew in the data. Conversely, such patterns are not discernible in most other resource use areas due to restricted service data usage. The utilisation of private healthcare and personal social services is comparable in each arm; however, definitive conclusions cannot be drawn due to the limited number of participants, although it may be possible to streamline data collection in similar trials in future as for some areas of service use no participant reported using these services.

Summary data for each of the five dimensions of the EQ-5D-5L are presented individually in *Report Supplementary Material 1*, *Tables 23–39*. For those who were able to self-report, at baseline, none of the participants had the worst health state for mobility. The overall median and mean scores were 1.75 and 1.5, respectively. These scores indicate that participants experienced slight problems with walking about. The mean score for self-care was 1.67, suggesting slight problems with washing or dressing, a conclusion supported by the median score of 1. At baseline, the mean score for usual activities slightly exceeded 2, while the median score was 1. These results indicate that some participants had problems with their usual activities, although the median score implies that the majority experienced no problems. The responses for pain and discomfort dimensions, with mean and median scores of 2.5 and 3, respectively, indicate moderate pain and discomfort. Responses by the anxiety and depression dimensions, with mean and median scores of 2.33 and 2, suggest slight levels of anxiety or depression. For the EQ-5D-VAS, at baseline, the mean and median scores were 63 and 60, respectively (with 100 denoting the best imaginable health and 0 representing the worst possible health). Baseline EQ-5D-5L utility values were 0.58 and 0.62 for mean and median, respectively, with 1 indicating full health and 0 equivalent to deceased. Due to the limited number of participants completing the EQ-5D-5L, it remains unclear if the severity of responses varied over the follow-up period.

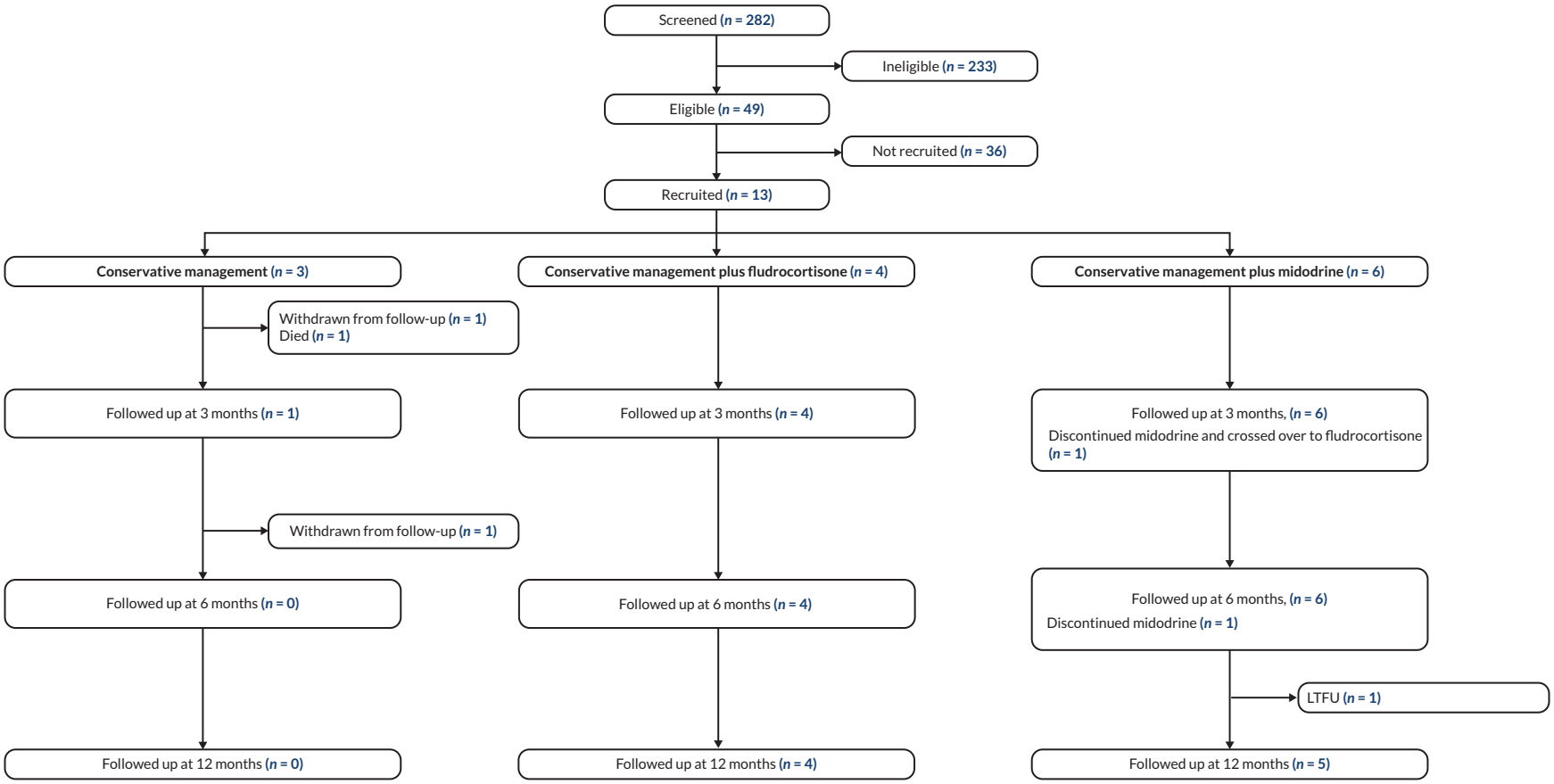

FIGURE 1 Consolidated Standards of Reporting Trials flow diagram. LTFU, lost to follow-up.

TABLE 4 Completion rates of outcome measures

	Conservative management	Conservative management plus fludrocortisone	Conservative management plus midodrine	Overall
Month 3[a]	Exp = 1	Exp = 4	Exp = 6	Exp = 11
BP[b]	Exp = 2	Exp = 4	Exp = 6	Exp = 12
Collected	1 (50%)	4 (100%)	6 (100%)	11 (92%)
Not collected	1 (50%)	0 (0%)	0 (0%)	1 (8%)
How was the BP obtained?				
Study visit	0 (0%)	4 (100%)	6 (100%)	10 (91%)
Other medical records	1 (100%)	0 (0%)	0 (0%)	1 (9%)
OHQ	1 (100%)	4 (100%)	6 (100%)	11 (100%)
NEADL	1 (100%)	4 (100%)	6 (100%)	11 (100%)
Falls diary				
Falls data collected	0 (0%)	4 (100%)	6 (100%)	10 (91%)
Falls diary completed	0 (0%)	2 (50%)	5 (83%)	7 (64%)
Month 6[a]	Exp = 0	Exp = 4	Exp = 6	Exp = 10
BP[b]	Exp = 2	Exp = 4	Exp = 6	Exp = 12
Collected	0 (0%)	4 (100%)	6 (100%)	10 (83%)
Not collected	2 (100%)	0 (0%)	0 (0%)	2 (17%)
How was the BP obtained?				
Study visit	N/A	4 (100%)	5 (83%)	9 (90%)
Other medical records	N/A	0 (0%)	1 (17%)	1 (10%)
OHQ	N/A	4 (100%)	6 (100%)	10 (100%)
NEADL	N/A	4 (100%)	6 (100%)	10 (100%)
Falls diary				
Falls data collected	NA	4 (100%)	6 (100%)	10 (100%)
Falls diary completed	NA	2 (50%)	4 (67%)	6 (60%)
Month 12[a]	Exp = 0	Exp = 4	Exp = 5	Exp = 9
BP[b]	Exp = 2	Exp = 4	Exp = 5	Exp = 11
Collected	0 (0%)	4 (100%)	5 (100%)	9 (82%)
Not collected	2 (100%)	0 (0%)	0 (0%)	2 (18%)
How was the BP obtained?				
Study visit	N/A	3 (75%)	5 (100%)	8 (89%)
Self-assessed at home	N/A	1 (25%)	0 (0%)	1 (11%)
OHQ	N/A	4 (100%)	5 (100%)	9 (100%)
NEADL	N/A	4 (100%)	5 (100%)	9 (100%)
Falls diary				
Falls data collected	N/A	4 (100%)	5 (100%)	9 (100%)
Falls diary completed	N/A	1 (25%)	4 (80%)	5 (56%)

a The number of expected (exp) CRFs at this visit (unless otherwise stated).
b Also expected for those that withdrew but allowed use of routinely collected medical data.

One participant provided EQ-5D-5L by proxy at baseline and 12 months, and two provided proxy data at 6 months. Due to the low number of participants, summary text is not provided.

Discussion/interpretation

This randomised controlled trial was not feasible as planned. The timing of the trial, originally planned to open to recruitment in 2020, was unfortunate as the effects of the COVID-19 pandemic had a severe impact on research sites. Several sites were unable to recruit due to staff redeployment, either to other clinical duties, or to focus on COVID-19 clinical trials. COVID-19 also had an impact on clinical pathways. Sites noted that an increase in virtual consultations resulted in fewer postural BP measurements and fewer diagnoses of OH. Delays to sponsorship and ethical permissions occurred as COVID-19 studies were prioritised.

From a recruitment perspective, the biggest barrier was the eligibility criteria which excluded participants who were taking, or had recently tried the medications under investigation, this amounted to just over half of screened participants. The second most common barrier was a contraindication to one of the study medications, which occurred in 20% of ineligible participants.

Of the 13 participants recruited, the primary outcome was available in 10. With such small numbers, it is difficult to estimate whether these figures would be helpful to estimate attrition in a larger study. One potential solution to reduce attrition at the primary end point would be to move this from 6 to 3 months. Indeed, looking at the individual results in *Appendix 1*, *Figure 2*, it appears that most of the change seen from baseline occurs at the 3-month time point, with little additional gain at 6 months. However, feedback from participants and from site investigators was that 6 months allows adequate time to titrate medication doses.

At the primary outcome time point (6 months), all participants from the control arm had withdrawn or died, in contrast to no withdrawals in the medication arms. Being randomised to the control arm was raised as a concern by some sites in their post-trial feedback, as some participants did not want to be allocated to control. This is an important factor to consider for future trials. However, it should be stressed that it remains unknown whether medication is superior to non-drug therapy, and this is an important question which needs answering. This concern is also at odds with previous patient and public involvement (PPI) work which prioritised treatment of OH without increasing medication burden.[21] This participant and clinician equipoise could be addressed through novel trial design. For example, a Personalised Randomised Controlled Trial (PRACTICAL) design allows randomisation to acceptable arms only, such that if a contraindication/exclusion to one intervention existed, the participant would not be randomised to that arm.[22] A blinded crossover trial is another option, but as one in five participants were excluded due to a contraindication, this design would also be affected by this.

The completion rates of the secondary outcomes were excellent at all time points for symptoms, activities of daily living, and BP. There were two exceptions. One was the completion rates of falls diaries. However, this is not unusual in the field of falls-related research. One participant fed back that they would have preferred an online falls diary, and this this should be explored as an option for future trials, with the possibility of completing all the outcomes remotely. The number of outcome measures in the trial was not considered too many by most participants. In fact, feedback from participants was very positive, with no negative experiences reported by respondents in the post-trial feedback. The second exception was the reporting of BP for those that withdrew but consented to the use of routinely collected medical data, this applies to two participants. For these participants, BP measurements were recorded, while enrolled; however, after withdrawing no measurements were reported. It is not clear if no measurements were available or if these were not obtained. For future trials, consideration may be needed on how to incorporate routinely collected data.

An additional uncertainty when developing the trial protocol was the expected level of crossover between intervention arms. Only one participant changed their allocated intervention arm. Unfortunately, the numbers of participants in the pilot were too low to provide robust data for future estimates, but as far as we are aware, it is the only current data available to inform this.

It is uncertain whether the trial may now be more feasible in the post-COVID-19 period. Modified clinical pathways are now established and there is a greater recognition that non-COVID-19 clinical services and research should continue even during future outbreaks (with safety measures in place). The trial was designed to be as pragmatic and flexible as possible, to match usual clinical pathways, to make recruitment and trial processes simpler for participants and clinician investigators. However, one of the limitations which became apparent was that there was considerable heterogeneity in usual

practice between sites, so the study pathways were not always easily deliverable for sites. In addition, while the pragmatic nature attempted to reduce the workload for sites, there was a lack of available research support at sites to help deliver the trial in clinical settings. There may be an argument for increased funding to provide more research support, rather than depending on clinicians to deliver pragmatic clinical trials.

It is more difficult to address the exclusion criteria of currently taking treatment which led to the exclusion of large numbers of people with OH. To include these participants would require a 'washout' period off treatment, to measure baseline outcomes, which may be considered unacceptable by some patients and clinicians. Furthermore, their inclusion would introduce bias, as previous exposure to treatment will influence an individual's assessment of treatment response, this is particularly relevant with the primary outcome being subjective. One solution would be to conceal treatment allocation in a placebo-controlled trial. However, participants and clinicians may be unwilling to stop treatment with the chance of being randomised to placebo. Alternatively, identifying treatment-naive people with OH could be done in primary care. However, the coding of OH in primary care is very poor (24,973 cases among 2,911,260 records over 10 years).[23] BP screening for OH in primary care is also unlikely to be an efficient recruitment method. Not all people with OH would require medication and screening for OH does not reflect current clinical practice and may produce skewed results. This has been seen in falls intervention research where interventions have been shown to be successful in those recruited from falls services, but not in those screened in primary care.[24,25]

Unfortunately, the low sample size does not provide a useful estimate of attrition or crossover rates to help inform future trial design. Although all the attrition occurred in the control arm at the primary end point, the numbers are too small to conclude that this resulted directly from allocation to control. Numbers are also too small to evaluate whether the study is inclusive off different ethnic backgrounds. All recruited participants were of a White background, but it is not possible to evaluate whether different strategies would be required in a future trial.

CONFORM-OH was the first clinical trial to be led by the Chief Investigator (CI) who completed the NIHR Clinician Scientist fellowship while securing funding for this trial. Alongside a team of experienced clinical trialists, the CI has gained valuable experience in clinical trial leadership in a population in whom clinical trials are more challenging. This is particularly important in the field of academic geriatrics where capacity building is urgently required and the delivery of clinical trials is more complex.

CONFORM-OH was designed to be a comprehensive within trial and model-based cost–utility analysis. Unfortunately, these plans were not realised due to the low rate of recruitment of study participants. However, the study has been substantially analysed as if it were a full economic evaluation. This was undertaken to provide training opportunities for an early-career health economist, including development of a comprehensive health economics analysis plan and the complete coding of participant data. This will allow this researcher to support future trials more efficiently.

Statistical support was provided by the Biostatistics Research Group (BRG) at Newcastle University. CONFORM-OH was the first funded trial within the BRG to use a multiarm multistage design. This allowed the BRG to strengthen processes in performing efficient interim analyses and considerations for blinding within the statistics team. The CONFORM-OH statistical and Clinical Trials Unit (CTU) co-applicants have utilised the knowledge gained from the CONFORM-OH trial in the NIHR funded robust interims for adaptive designs project. This is part of a growing programme of work by BRG and CTU teams to develop innovative adaptive trials, building capacity to address complex questions such as posed in CONFORM-OH, and that arise in many of the therapeutic areas we study. CONFORM-OH was also the first trial within the BRG to frame the Statistical Analysis Plan within the estimand framework. The knowledge and learning gained from this have been shared across the BRG and CTU which will benefit future NIHR funded trials.

Patient and public involvement

This study builds on previous PPI work in which people with OH prioritised the treatment of OH to improve their quality of life, but specifically without increasing their medication burden.[21] The inclusion of a conservative treatment arm was therefore important to determine whether non-drug therapies were as clinically effective as medication. However, feedback from site investigators shows that for some people with OH, the possibility of being randomised to non-drug therapies was a barrier to recruitment.

The CONFORM-OH study included two people with OH on the TSC and a Research Assistant who worked as a link between the TSC and the PPI members. During development of the study, people with OH stressed the

importance of having people with OH involved in the study, but there were concerns that their symptoms would prevent them attending regular meetings, and they reported that they lacked confidence to attend formal meetings. The PPI link provided the PPI members with updates and attended their home, helping them dial-in to TSC meetings. The PPI members also worked with the PPI link in their own homes to develop and review patient information sheets, consent forms and other documents such as instructions on measuring BP at home.

As the CONFORM-OH study was in set-up in early 2020, it was adversely affected by the COVID-19 pandemic. At this stage, the PPI members provided key expertise. Their input informed us that many people who may be eligible for the study, would not feel confident to attend research visits, particularly as news reports were describing inadequate provision of personal protective equipment. At this stage, study set-up was paused, and the PPI members were involved in modifying the protocol to make participants feel safer; including allowing participants to measure their own BP at home, being more flexible around the timing of research visits and allowing virtual consultations.

Unfortunately, one of our PPI experts withdrew from the TSC due to ill health. The second PPI expert also had progression of their illness and although they did continue to provide input into the study, it was minimal. At this point, the pilot had drawn to an end, and it was decided not to recruit further PPI experts at that stage.

Future studies should consider the involvement of both people with OH and their carers or family members who may be less susceptible to the effects of chronic disease and frailty over the course of a clinical trial. The involvement of older and frailer people of OH should still be a central part of the study team to facilitate protocol design to include the most excluded groups.

Equality, diversity and inclusion

Older people, people with multiple long-term conditions (MLTC) and people with frailty are the biggest users of the NHS but are typically excluded from clinical research, leading to a serious inequality paradox in health care.[26] The CONFORM-OH trial was specifically designed to increase participation from these groups, providing an evidence base for those who usually do not have evidence to inform treatment.

It is important not to include too many research assessments as this population already has a high clinical appointment burden. To make it easier to include and retain older people and people with MLTC the protocol was designed to allow research outcomes to be measured at usual clinic appointments. To facilitate this, the protocol allowed larger flexibility around the timing of outcome measurement, allowed virtual consultations and allowed the use of routinely collected data. Having academic geriatricians and including older people in the design and management of the research meant that appropriate language and terminology were used in the study. This was important as terms such as ‘the elderly’ and ‘the frail’ are barriers to including older people in clinical trials.

Although the recruitment numbers are very small, the mean age of participants was 74 years (SD 9.6), the median symptom score was 6.2 (range 3.8–8.8) (this is much higher than other clinical trials involving people with OH), the median NEADL score was 18 (range 2–22), which indicates that all participants required some level of support for self-care.[27–29] This is reassuring as it suggests the trial design was inclusive for older and frailer groups of people, more so than previous trials in this field which focus on the rarer forms of the disease in younger single-pathology cohorts.

Impact and learning

When designing clinical trials in the post-COVID era, consideration must be given to changes in clinical services. Remote consultations are now more common, which does not fit with more traditional clinical trial design. Remote consultations also limit the collection of some clinical outcomes such as postural BP. Future trials will need to consider increased funding and support to enable home visits to collect key outcomes, which is particularly relevant in this cohort who are affected by frailty and multi-morbidity.

Improved recording and coding of postural BP and OH would help identify more potential research participants. When preparing the application for funding for CONFORM-OH, a review of six Primary Care Practices (34,085 patients) identified only 395 cases of OH due to poor coding. The generally poor coding of OH in primary and secondary care limits the potential for the use of routinely collected clinical data to answer research questions in this area. This is also limited by the generally inconsistent recording of postural BP in clinical records. A more standardised approach to the recording the diagnosis and assessment of OH could assist with future research.

Although not a significant barrier to the trial, a lack of equipoise amongst clinicians was more prevalent than expected. At least one site declined to participate as the PI was not willing for their patients to be randomised to midodrine before trying fludrocortisone. Other PIs, when faced with patients with severe OH, were unwilling for their patients to be randomised to the conservative arm.

Given the recruitment difficulties, more novel trial designs are needed to answer the research question. The exclusion criteria of currently or recently taking one of the trial drugs would need to be addressed. Current or recent use of a trial drug would introduce bias in an open-label study, while the chance of being randomised to placebo for an individual already on treatment may not be considered as acceptable. To address the aforementioned equipoise, more novel designs may allow randomisation to selected arms to prevent allocation to an 'unacceptable' arm.

The impact of COVID-19 was felt acutely by the study team. As a clinical trial within the field of Geriatric Medicine, it was particularly vulnerable as the majority of Principal Investigators were geriatricians and general physicians. As such, they were at increased risk of redeployment and unable to work on the study. Geriatric Medicine is an area where research infrastructure is not as well established as in other areas. With less robust infrastructure it is more susceptible to the impact of clinical pressures. There is an argument that greater research support should be provided to areas which are less experienced with research, but where research is greatly needed such as Emergency Medicine, General Medicine and Geriatric Medicine.

The biggest impact to arise from this study will be the use of the pilot data to inform the design of future clinical trials in this population. This should improve the efficiency and economy of future trials in this field as the research question remains important and unanswered. In the meantime, it is important to note that the interventions under evaluation should continue to be used in routine care, as an absence of evidence, is not an absence of effectiveness.

Implications for decision-makers

The timing of the trial was significantly impacted by the outbreak of COVID-19, which coincided with recruitment start date (December 2019). While this is not a specific outcome of this trial, the impact on this trial can be used, in the wider context, to guide response/policy to similar future events (including large influenza outbreaks). The points that contribute are redeployment of clinical staff to clinical duties, redeployment of research staff to COVID-19 studies and prioritisation of COVID-19 studies by Medicines and Healthcare products Regulatory Agency, Research Ethics Committee committees and Sponsor.

More work is needed to develop research capacity to deliver more complex clinical trials. This is particularly relevant in studies involving older people and people with MLTC. This could include more training opportunities for early career researchers and capacity building for existing principal investigators (PIs) considering involvement in clinical trials involving older people. The NIHR Clinical Research Network for Ageing studies has been delivering such strategies and their work could be expanded and built upon.

More incentives for teams to take on more complex studies has the potential to improve delivery of complex clinical trials. At present, the system favours simple studies and disincentivises studies that are more complex to deliver. For example, the consent process can be more involved if capacity assessments are required, adverse events are more likely to occur with increasing age and frailty. When competing for sites and PIs to deliver trials, easier to deliver studies are more likely to be considered.

Research recommendations

A study to answer this research question should be re-designed using more flexible and novel methods such as PRACTICAL design, where participants can be excluded from some intervention arms but randomly assigned to others.[22] An alternative method to improve efficiency could be a 2 × 2 factorial design, including combination treatment with fludrocortisone plus midodrine. However, it would not be feasible to include 12-month falls data for this design, and as 20% of potential participants had a contraindication to one of the medications, the PRACTICAL design may be preferable. To improve efficiency, the primary end point could be shortened to 3 months. Given the difficulty recruiting to CONFORM-OH, an international trial should be considered to increase recruitment.

Research visits in parallel to clinical visits may improve clinical staff ability to support clinical research. This may also address the issue of heterogeneity between services by standardising the research visits.

A registry of people with OH to support future research should be considered. Given how common the condition is and the lack of good-quality evidence, such a registry could be very valuable.

More work is needed to develop research capacity to deliver more complex clinical trials. This is particularly

relevant in studies involving older people and people with MLTC. To do this, the work of the Ageing Clinical Research Network to support local PIs, can be expanded upon. There could be more incentives for teams to take on more complex studies. At present, the system favours simple studies and disincentivises studies that are more complex to deliver.

Conclusions

This pilot randomised controlled trial provides useful data to support the design of a future clinical trial. A novel trial design is likely to improve the success of a future trial. The inclusive and pragmatic selection criteria were no barrier to including individuals with frailty, but prior exposure to an intervention was a significant barrier to recruitment. The redeployment of clinical and academic staff during and after the COVID-19 pandemic, which reduced sites' capacity to recruit, was an untimely and unfortunate barrier to site set-up and recruitment. Adequate funding and resource must be available to support clinical research involving people with frailty and MLTC, particularly in research naïve areas where research is not routinely practised.

Additional information

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Susan Shenkin: Supervision.

Ruth Pearce: PPI contributions.

Data-sharing statement

A de-identified data set 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. All data requests should be submitted to the corresponding author for consideration.

Ethics statement

The study was given approval by the UK NHS Health Research Authority's Newcastle and North Tyneside 1 Research Ethics Committee (reference 21/NE/0083) on 15 June 2021.

Information governance statement

The Newcastle Upon Tyne Hospitals NHS Foundation Trust (NUTH) and Newcastle University are committed to handling all personal information in line with the UK Data Protection Act (2018) and the European Union General Data Protection Regulation 2016/679. Under the Data Protection legislation, NUTH is the Data Controller, information about how personal data is handled, including how to exercise individual rights and the contact details for the Data Protection Officer can be found on the Newcastle Hospitals NHS Foundation Trust website (www.newcastle-hospitals.nhs.uk). The data processor, Sealed Envelope Ltd (Company No. 4338315), was contracted to provide an internet-based randomisation service and an internet-based Red Pill software application for collection and management of research study data.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/HGRW7249.

Primary conflicts of interest: Helen Mossop reports grants. Miles Witham reports grants, panel membership [HTA Prioritisation Committee A (out of hospital)] and is vice president for research for the British Geriatrics Society. James MS Wason reports grants. Alison J Yarnall reports grants and has previously received funding and/or honoraria from Britannia, UCB, Abbvie, GSK, Teva-Lundbeck, GE Healthcare and Genus for attending educational events and chair of trial DSM board. Helen Hancock reports grants. James Frith reports grants (NIHR HTA), panel membership (HTA PCCPI Panel and HTA Prioritisation Committee B) and links with industry (Isotech Ltd).

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This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Trial registration

This trial is registered as ISRCTN87213295.

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Award publications

This synopsis provided an overview of the research award *A comparison of fludrocortisone, midodrine or usual care to treat orthostatic hypotension a multi-arm multi-stage randomised controlled trial: CONFORM-OH*. Other articles published as part of this thread are:

Mossop H, Al-Ashmori S, Sotire T, Clark E, Watson G, Witham MD, *et al*. Control, Fludrocortisone or Midodrine for the treatment of Orthostatic Hypotension (CONFORM-OH): results from an internal pilot randomised controlled trial. *Pilot Feasibility Stud* 2025;**11**:118. https://doi.org/10.1186/s40814-025-01704-7

For more information about this research, please view the award page (www.fundingawards.nihr.ac.uk/award/NIHR127385).

About this synopsis

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List of supplementary material

Report Supplementary Material 1
Health and social services utilisation data: Tables 1–22: Summary of health and social services utilisation data, Tables 23–39: Summary data for each of the five dimensions of the EQ-5D-5L

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/HGRW7249).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

The supplementary materials (which include but are not limited to related publications, patient information leaflets and questionnaires) are provided to support and contextualise the publication. Every effort has been made to obtain the necessary permissions for reproduction, to credit original sources appropriately, and to respect copyright requirements. However, despite our diligence, we acknowledge the possibility of unintentional omissions or errors and we welcome notifications of any concerns regarding copyright or permissions.

List of abbreviations

BP	blood pressure
BRG	Biostatistics Research Group
CONFORM-OH	Control, Fludrocortisone or Midodrine for the treatment of Orthostatic Hypotension
CTU	Clinical Trials Unit
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
EQ-5D-VAS	EuroQol-5 Dimensions visual analogue scale
HTA	Health Technology Assessment
MLTC	multiple long-term conditions
NEADL	Nottingham Extended Activities of Daily Living
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NUTH	The Newcastle Upon Tyne Foundation Trust
OH	orthostatic hypotension
OHQ	Orthostatic Hypotension Questionnaire
PD	Parkinson's disease
PI	principal investigator
PRACTICAL	Personalised Randomised Controlled Trial
PPI	patient and public involvement
TSC	Trial Steering Committee

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Appendix 1

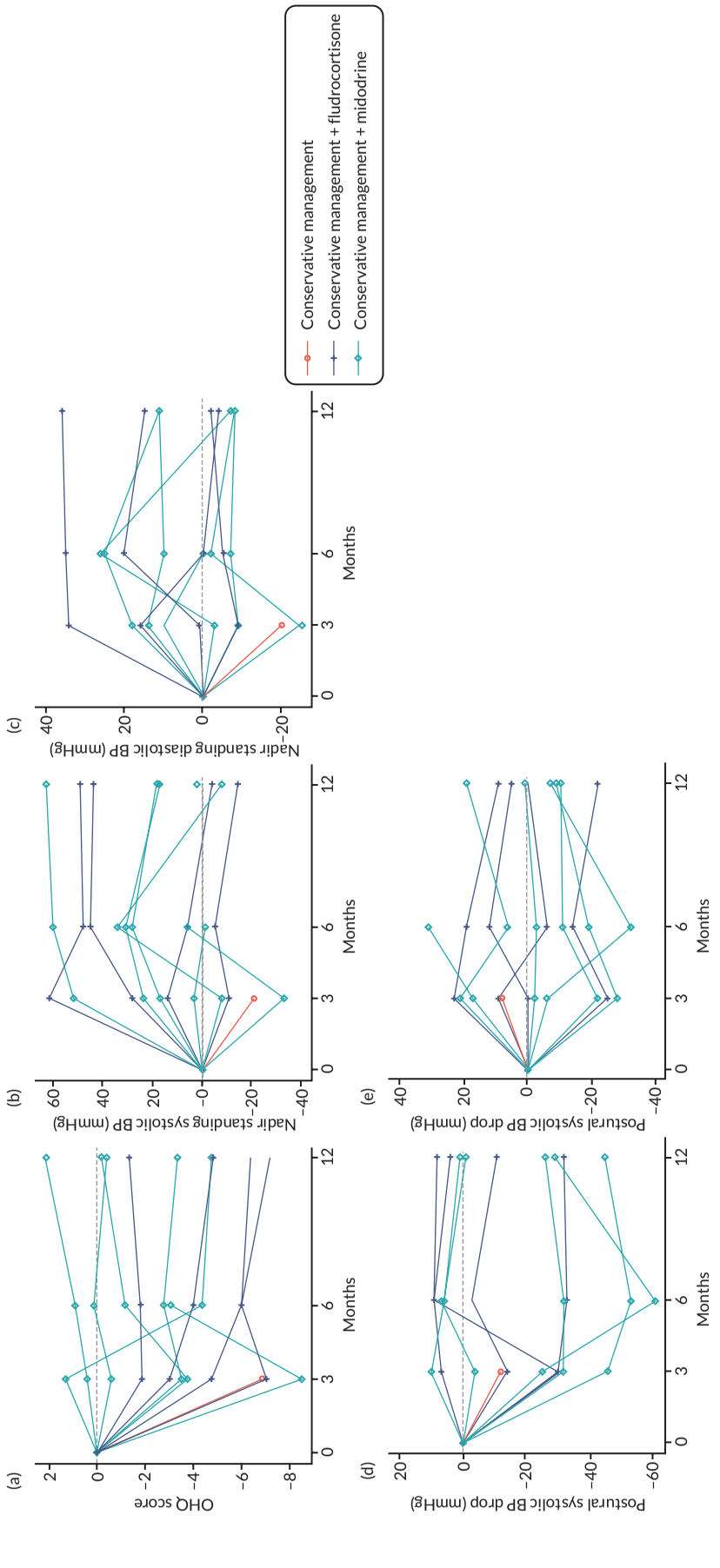

FIGURE 2 Individual outcome data plots.

TABLE 5 The frequency of non-drug therapies used per site and participant

	Number of sites	Number of participants
Trigger avoidance (e.g. standing safely, avoiding alcohol etc.)	4	10
Hydration	4	13
Bolus water drinking	2	6
Salt intake	2	7
Caffeine intake	2	2
Physical counter-manoeuvres	3	8
Provision of compression stockings (grade 2) – below knee	1	1
Provision of compression stockings (grade 2) – full length	0	0
Abdominal compression	0	0
Medication review	2	6
Other – advised to consider stockings from GP	1	4

GP, general practitioner.

TABLE 6 Changes from baseline in primary and secondary outcome measures

	3-month follow-up			6-month follow-up			12-month follow-up		
	Conservative management	Conservative management plus fludrocortisone	Conservative management plus midodrine	Conservative management	Conservative management plus fludrocortisone	Conservative management plus midodrine	Conservative management	Conservative management plus fludrocortisone	Conservative management plus midodrine
	N = 1	*N* = 4	*N* = 6	*N* = 0	*N* = 4	*N* = 6	*N* = 0	*N* = 4	*N* = 5
OHQ									
Mean (SD)	−6.9 (.)	−4.2 (2.2)	−2.4 (3.6)	N/A	−4.5 (2.0)	−1.7 (2.0)	N/A	−4.9 (2.6)	−1.3 (2.7)
Median (range)	−6.9 (−6.9 to −6.9)	−3.9 (−7.0 to −1.9)	−2.1 (−8.5 to 1.3)	N/A	−5.0 (−6.0 to −1.8)	−2.0 (−4.4 to 0.9)	N/A	−5.6 (−7.2 to −1.3)	−0.4 (−4.8 to 2.2)
NEADL									
Mean (SD)	−6.0 (.)	2.3 (9.0)	−0.3 (4.1)	N/A	3.3 (8.8)	−1.0 (3.2)	N/A	3.3 (8.7)	−0.8 (3.7)
Median (range)	−6.0 (−6.0 to −6.0)	0.0 (−6.0 to 15.0)	0.5 (−8.0 to 3.0)	N/A	0.5 (−4.0 to 16.0)	−0.5 (−7.0 to 2.0)	N/A	0.0 (−3.0 to 16.0)	−1.0 (−4.0 to 5.0)
Nadir standing BP									
Systolic									
Mean (SD)	−21.0 (.)	23.3 (30.5)	9.2 (29.1)	N/A	23.5 (27.0)	26.3 (21.8)	N/A	18.8 (32.4)	18.4 (27.2)
Median (range)	−21 (−21 to −21)	21 (−11 to 62)	10 (−33 to 52)	N/A	26 (−5 to 48)	30 (−1 to 60)	N/A	20 (−14 to 49)	17 (−8 to 63)
Diastolic									
Mean (SD)	−20.0 (.)	10.5 (18.7)	0.8 (16.3)	N/A	12.5 (18.5)	8.7 (14.2)	N/A	11.3 (18.6)	−0.2 (10.2)
Median (range)	−20 (−20 to −20)	9 (−9 to 34)	4 (−25 to 18)	N/A	10 (−5 to 35)	5 (−7 to 26)	N/A	7 (−4 to 36)	−7 (−8 to 11)
Postural BP drop									
Systolic									
Mean (SD)	−12.0 (.)	−17.0 (17.8)	−14.5 (23.3)	N/A	−4.5 (19.8)	−21.2 (31.6)	N/A	−7.8 (18.1)	−20.0 (19.6)
Median (range)	−12 (−12 to −12)	−22 (−31 to 7)	−15 (−46 to 10)	N/A	3 (−33 to 9)	−13 (−61 to 7)	N/A	−4 (−32 to 8)	−26 (−45 to 1)
Diastolic									
Mean (SD)	8.0 (.)	1.8 (20.2)	−3.3 (19.9)	N/A	2.8 (15.3)	−4.7 (21.8)	N/A	−2.0 (13.8)	−1.2 (12.1)
Median (range)	8 (8 to 8)	5 (−25 to 23)	−4 (−28 to 21)	N/A	3 (−14 to 19)	−7 (−32 to 31)	N/A	3 (−22 to 9)	−7 (−10 to 19)

This synopsis should be referenced as follows: Mossop H, Al Ashmori S, Sofire T, Clark E, Watson G, Witham M, *et al.* Control, Fludrocortisone or Midodrine for the treatment of Orthostatic Hypotension: CONFORM-OH pilot RCT and economic evaluation. *Health Technol Assess* 2025;**29**(54). https://doi.org/10.3310/HGRW7249