CONFORM-OH

Clinical Trial Protocol

Full Title: **Con**trol, **F**ludrocortisone **or M**idodrine for the treatment of **O**rthostatic **H**ypotension: A Randomised Controlled Trial
Short Title/Acronym: CONFORM-OH
Protocol Version Number & Date: V5.0, 08 July 2022

This protocol has regard for the HRA guidance.

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PROTOCOL APPROVAL SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted. The Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the relevant Standard Operating Procedures (SOPs) and other regulatory requirements as required.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Representative of the Research Sponsor

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Position:

Signature: Date:

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Signature: Date:

PROTOCOL ACCEPTANCE SIGNATURE PAGE

Short Trial Title: CONFORM-OH **Site Name:**

Site I.D. Number:

Principal Investigator

I have carefully read and understood protocol version 5.0. I agree to conduct the trial in compliance with the Protocol, Good Clinical Practice and all required regulatory requirements.

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Trial Website:	https://research.ncl.ac.uk/conform-oh/

TRIAL SUMMARY

Trial Title	**Con**trol, **F**ludroc**or**tisone or **M**idodrine for the treatment of **O**rthostatic **H**ypotension: A Randomised Controlled Trial	
Acronym	CONFORM-OH	
Clinical Phase	IV	
Trial Design	Pragmatic, open label, randomised, prospective, superiority, multi-arm, multi-stage clinical trial with a 10-month internal pilot.	
Participant Population	Adults with symptomatic orthostatic hypotension receiving treatment in secondary care.	
Planned Sample Size	366 (122 per arm) will be consented and randomised. An interim analysis will be performed after the 200th participant has been randomised, at which point a decision will be made whether to drop or continue one (or all) treatment arms.	
Treatment Duration	12 months	
Follow-up Duration	12 months	
Planned Trial Period	4.5 years (54 months) in total, 30 months' recruitment with approximately 12 months' follow-up and 12 months' data cleaning and analysis.	
Research Aim	This trial will evaluate the clinical and cost effectiveness of three different treatment strategies for orthostatic hypotension.	
	Objective	**Outcome Measure**
Primary	To determine whether the treatment strategies of conservative management plus fludrocortisone, and conservative management plus midodrine improve symptoms of OH compared to conservative management alone.	Change in the Orthostatic Hypotension Questionnaire (OHQ) score at six months.
Secondary	To determine how the treatment strategies of conservative management plus fludrocortisone, and conservative management plus midodrine affect the following outcomes compared to conservative management alone over a 12-month period: 1. Health-related quality of life measured by the EQ-5D-5L 2. Activities of daily living (ADLs) measured by the Nottingham Extended ADL scale	

	3. Falls (number of falls, number of fallers/non-fallers, fall rate per person year, time to first fall, fall-related injuries, number of syncopal events) 4. Standing blood pressure and postural blood pressure drop 5. Quality adjusted life years (QALYs) estimated from responses to the EQ-5D-5L 6. Costs to the NHS, personal social services and patients 7. Cost-effectiveness of each treatment strategy from a patient and NHS and personal social services perspective at 12 months measured in terms of the incremental costs per QALY gained 8. Side effects and the safety data associated with each treatment strategy
Inclusion Criteria	• Adults aged 18 years and over • A clinical diagnosis of symptomatic OH which is either: 1. Clinically significant where you would wish to start treatment quickly without a trial of lifestyle modification, OR 2. Refractory to an adequate period of lifestyle modification (to be judged clinically) • A drop in systolic blood pressure of ≥20mmHg and/or a drop in diastolic blood pressure of ≥10mmHg, within three-minutes of standing upright from a supine position (or on tilt-testing) which has been obtained in the preceding eight weeks. • A score of ≥2 on the OHQ • Willing and able to provide informed consent prior to any trial procedures taking place.
Exclusion Criteria	• OH secondary to acute or reversible causes (e.g. haemorrhage, sepsis) • Use of fludrocortisone or midodrine within the last six months • Terminal illness or life expectancy <12 months • Supine hypertension (where the risks of treatment outweigh the benefits) at baseline • A known allergy to study medication • A known contra-indication to fludrocortisone or midodrine which outweighs the potential clinical benefit (i.e. if in usual clinical care the clinician and participant feel the risks outweigh the benefits, they would be excluded) • Current or planned pregnancy during the trial period, or breast feeding (If randomised to either pharmacological arm the participant, if female and of child-bearing potential, must have a negative pregnancy test [urine beta-human chorionic gonadotropin (β-hCG)] and are required to use a highly effective contraceptive method during the trial)

	• Inability to communicate in English • Inability to comply with the study procedures as specified in the schedule of events. • Currently taking part in another clinical trial that would interfere with the outcomes of CONFORM-OH
Intervention & Investigational Medicinal Products	1. Control: Non-pharmacologic therapy (conservative management) 2. Conservative management plus fludrocortisone (50 to 400 mcg tablet(s) daily, titrated according to clinical response) 3. Conservative management plus midodrine (2.5 mg BD to 10 mg tablet(s) TDS, titrated according to usual clinical response)

Contents

Glossary of Abbreviations

ABBREVIATION	DEFINITION
ADL	Activities of Daily Living
AE	Adverse Event
AR	Adverse Reaction
BNF	British National Formulary
BP	Blood pressure
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
DLB	Dementia with Lewy bodies
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
eCRF	electronic Case Report Form
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HRA	Health Research Authority
HTA	Health Technology Assessment
ICF	Informed Consent Form

ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
ITT	Intention-to-treat
IMP	Investigational Medicinal Product
ISF	Investigator Site File
LPLV	Last Patient Last Visit
LSBP	Lying and Standing Blood Pressure
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale
MHRA	Medicines and Healthcare products Regulatory Agency
MSA	Multiple System Atrophy
NCTU	Newcastle Clinical Trials Unit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OH	Orthostatic Hypotension
OHQ	Orthostatic Hypotension Questionnaire
PD	Parkinson's Disease
PI	Principal Investigator
PIL	Participant Information Leaflet
PP	Per-Protocol
PROMS	Participant-Reported Outcome Measures
PSS	Personal Social Services
QA	Quality Assurance
QALY	Quality adjusted life year
R&D	Research & Development
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDS	Ter Die Sumendum (to be taken three times a day)
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File

1. Background and Rationale

1.1 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 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 US, the presence of OH in people with PD is known to increase overall health care-related costs 2.5-fold compared to those who have PD without OH ($25,205 ± $6546 vs. $9831 ± $4167/person/year)[5]. Similar data are not available for the UK and the applicability of these data to the NHS is limited.

The reduction in standing BP results in decreased perfusion of the brain, leading to a wide variety of non-specific symptoms including dizziness, headache, nausea, fatigue and visual disturbance; at its most severe it can cause falls and syncope (fainting) [6]. There are also longer-term sequelae, with OH increasing the risk of stroke, cognitive impairment and all-cause mortality [7, 8]. People with OH have a reduced quality of life due to the difficulties in performing even simple tasks which involve standing, such as teeth brushing, making a drink or answering the door. OH is closely associated with falls, particularly in older people, where in addition to the direct physical harms, the fear of falling can cause significant physical, psychological and social morbidity [9]. However, for people with OH, it is their symptoms which cause the most significant reduction in quality of life [10].

1.2 Rationale

Despite the high prevalence of OH, there is very little good quality evidence to support its management, creating a huge unmet clinical need [11]. NICE provides evidence summaries for fludrocortisone and midodrine when used for OH, but notes that long-term efficacy and safety is unclear [12, 13]. NICE also comments that these studies are limited by their use of disease-centred outcomes (i.e. blood pressure) rather than patient-centred outcomes, such as symptoms and quality of life. Furthermore, these studies use very selective patient cohorts that are not representative of those seen in practice, i.e. those with multi-morbidity.

In 2015, a licence was granted by the MHRA for the use of midodrine in the UK. As of February 2021, it is the only licenced medication for 'severe OH due to autonomic dysfunction when corrective factors have been ruled out and other forms of treatment are inadequate'. Prior to 2015, its use was limited to only a few centres in the UK and therefore clinical experience with this drug is lacking in comparison to fludrocortisone. The 2017 NICE guidelines on Parkinson's disease in adults recommends that clinicians consider using midodrine for OH, or if this is contraindicated or ineffective, to consider fludrocortisone. The guideline specifies that this recommendation is based on very low-quality evidence and the opinion of the guideline group. However, in reality this recommendation has not translated into clinical practice; clinicians tend to use midodrine only if fludrocortisone has been ineffective [14-16].

Following conservative measures including physical counter manoeuvres and fluid and salt loading, the European Society of Cardiology recommends the use of midodrine and 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 [17]. Similarly, systematic reviews and meta-analyses consistently describe existing

evidence as poor quality, calling for more rigorous evaluation to guide clinical practice [17-21]. Fludrocortisone is perhaps used more commonly than midodrine in clinical practice, but it may result in higher rates of hospitalisation than midodrine [22, 23]. Both agents have side effects (>1 in 10 for midodrine [24]), but as their relative effectiveness is unclear, it is unknown whether the benefits outweigh their harms.

The cost of medications for OH is modest, but the cost consequences of successful treatment and for the management of side effects are not known. No high-quality economic evaluations directly applicable to the NHS comparing these interventions with each other or against current practice have been identified. Recent guidance from the Scottish Medicines Consortium suggests that there is a small budget impact of midodrine based on expenditure and prescribing data but this estimate does not appear to include longer term impacts [25]. Similar data for fludrocortisone are not available. Therefore, the lack of evidence on the relative cost-effectiveness of fludrocortisone and midodrine means that the NHS lacks sufficient evidence about which of these two therapies represents a good use of scarce NHS resources.

1.3 Commissioned Call

Given the lack of robust evidence on the clinical and cost-effectiveness of treatment strategies in OH, patients and clinicians face considerable uncertainty in its management. The NIHR Health Technology Assessment (NIHR HTA) Programme commissioned research on the management of OH. CONFORM-OH has been funded by NIHR HTA and the protocol designed in line with the commissioning brief.

1.4 Risk Assessment/Evidence of Safety

This trial evaluates three strategies of care, which are current routine clinical pathways. All three treatment arms are recommended in clinical guidelines. None are known to have any superiority over another. Therefore, little additional risk will arise from the study interventions as would normally occur in clinical practice. Although fludrocortisone is used off-licence, it is used routinely in clinical practice for OH and has a dose recommendation in the British National Formulary (BNF).

This trial is categorised as: Type A = no higher than the risk of standard clinical care.

2 OBJECTIVES

This trial will evaluate the clinical and cost-effectiveness of three different strategies of care for the treatment of OH:

I. Control: Conservative management (non-pharmacologic treatments)
II. Intervention: Conservative management plus fludrocortisone
III. Intervention: Conservative management plus midodrine

2.1 Primary Objective

To determine whether the treatment strategies of conservative management plus fludrocortisone, and conservative management plus midodrine improve symptoms of OH compared to conservative management alone, measured by change in the Orthostatic Hypotension Questionnaire (OHQ) score at six months.

2.2 Secondary Objectives

To determine how the treatment strategies of conservative management plus fludrocortisone, and conservative management plus midodrine affect the following outcomes compared to conservative management alone over a 12-month period:

1. Health-related quality of life measured by the EQ-5D-5L
2. Activities of daily living (ADLs) measured by the Nottingham Extended ADL scale
3. Falls (number of falls, number of fallers/non-fallers, fall rate per person year, time to first fall, fall-related injuries, number of syncopal events)
4. Standing blood pressure and postural blood pressure drop
5. Quality adjusted life years (QALYs) estimated from responses to the EQ-5D-5L and data derived from the literature
6. Costs to the NHS, personal social services and patients
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
8. Side effects and the safety data associated with each treatment strategy

2.3 Exploratory Objective

An exploratory objective will be to compare the clinical effectiveness of fludrocortisone with midodrine at six months. However, as one of the treatment arms may be withdrawn following the interim analysis, this analysis may be limited to a relatively small sample size (minimum 67 in each arm).

3. TRIAL DESIGN

3.1 Summary of Trial Design

CONFORM-OH is a pragmatic, multi-arm, multi-stage, parallel group, prospective, randomised, open label, superiority trial, with a 10-month internal pilot.

OH is associated with long-term conditions, frailty and ageing. The target study population is therefore at an increased risk from the COVID-19 pandemic. This is a pragmatic trial and is designed to be delivered within routine clinical care, to minimise additional research visits and exposure to any

potential risk and burden. The trial design will accommodate variation in clinical practices and consultation methods to optimise recruitment and retention whilst ensuring data integrity and quality required to undertake a robust analysis.

Participants with OH will be randomised to usual care (conservative management), conservative management plus fludrocortisone or conservative management plus midodrine. Once treatment has been allocated, participants' care will follow usual local clinical practice for the allocated treatment over 12 months. Follow-up will be for a total of 12 months, with outcomes assessed at three, six and 12 months after randomisation.

After the 200th participant has been randomised an interim analysis will be performed based on the available three- and six-month outcomes. If a treatment arm is found to be inferior to the control arm it will be recommended to be dropped from the study (see Section 8 Statistical Considerations for further details), with control (conservative management) and the alternative treatment arm continuing to the planned randomisation target of 366 participants in a 1:1 ratio. If both study arms are inferior to control the study will stop. Recruitment will continue to all three arms while the interim analysis is being conducted.

3.2 Pilot

The 10-month internal pilot aims to address the following uncertainties:

i. Can a sufficient number of eligible patients be identified and recruited in 10 months, to make the trial viable over the planned 30-month recruitment period?
ii. Is the attrition rate of participants in line with the estimation used in the sample size calculation?
iii. Do adequate numbers of participants remain on allocated therapy at three and six months' follow-up?

3.2.1 Pilot Sites

We will aim to open an initial six sites during the first six months of the pilot. Thereafter, we will aim to open an additional 14 sites, to 20 trial sites in total. With an estimated randomisation rate of 0.8 participants per site per month, this will result in approximately 64 participants by the end of the 10-month pilot. Of these, we anticipate approximately 19 will have six-month primary outcome data and approximately 35 will have three-month outcome data.

3.2.2 Progress Criteria

Outcomes will be reviewed as a whole rather than as individual stop/go criteria. The following traffic light guidance will be used in the progress decision-making process:

i. Recruitment
    a. Monthly screening and recruitment figures will be monitored by the CTU to identify potential problems or site-specific issues, in order to address these in a timely manner over the course of the pilot (and throughout the full study). This will be achieved using an electronic screening log, integrated in Sealed Envelope, which will detail numbers of eligible patients, proportion of eligible patients approached for consent, proportion of eligible patients not approached and reasons why. Data will also be collected on

the proportion of patients randomised who do not receive the randomly allocated treatment and reasons why.

i. Green: 64 participants randomised over 10-month pilot (or ≥0.8 participants per site per month if there are delays in site opening)
ii. Amber: 40 to 64 participants randomised during 10-month pilot (or ≥0.5 to<0.8 participants per site per month if there delays in site opening)
iii. Red: ≤40 participants randomised during the 10-month pilot (or <0.5 participants per site per month if there are delays in site opening)

ii. Attrition
   a. Green: ≤15% of participants withdraw within six months of treatment allocation during the pilot, in line with estimated attrition rates
   b. Amber: 16 to 35% of participants withdraw during the pilot but with strategies identified to improve study retention
   c. Red: >35% of participants withdraw during the pilot; no identifiable solution to improve this to 15%

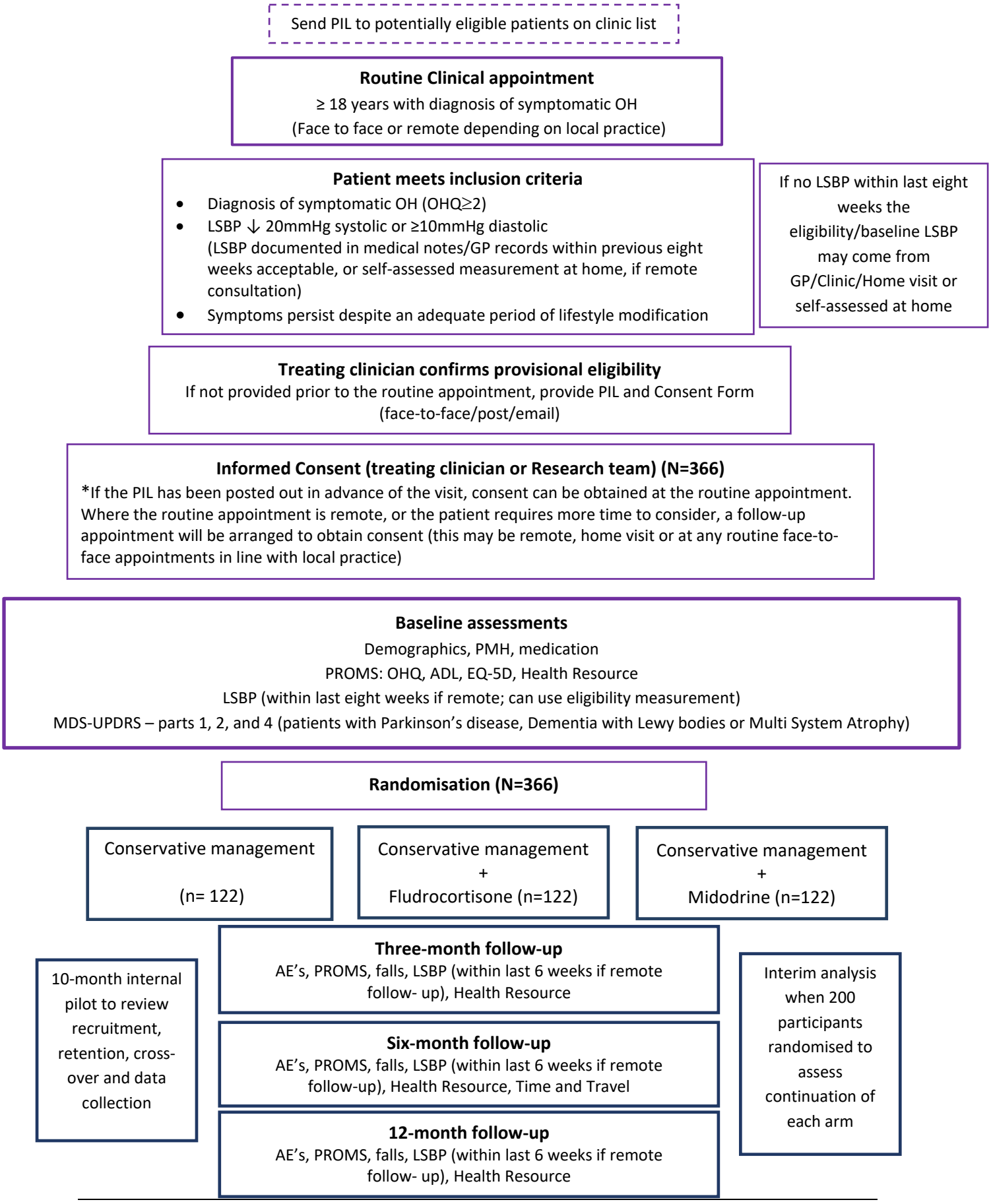
iii. Intervention cross-over
   a. Given the lack of available data on potential issues such as cross-over and 'off protocol intervention', we do not propose quantitative progression criteria. Rather this will be monitored and recorded, with the data reviewed during progress decision making.

iv. Outcome data
   a. Due to the pragmatic trial design and potential variation in clinical practice following the COVID-19 pandemic we will monitor the completeness and quality of the outcome data closely, to identify and address problems with outcome measures or data collection methods. It is unlikely that this will influence progression, but it will perhaps improve the quality of the data collection methods.

3.2.3 Progression

The pilot data will be reviewed by the TMG, DMC and TSC and their recommendations will be discussed with the funder (NIHR HTA), to determine whether the pilot progresses to full trial. Recruitment and trial procedures will continue during the decision process.

3.3 Flow Chart of Research Activity



3.4 Primary and Secondary Endpoints/Outcome Measures

3.4.1 Primary Outcome Measure and Endpoint

The primary outcome will be change in OH related symptoms measured using the Orthostatic Hypotension Questionnaire (OHQ), from baseline to six months.

The OHQ is composed of two sections: the first section consists of six questions, which rate the severity of six different symptoms on a scale of 0 to 10 [6]. The second section is composed of four question, which rates the impact of symptoms on standing and walking, on a scale of 0 to 10.

Scoring the OHQ: The OH Symptom Assessment score is calculated as an average of the responses to the six questions on the OH Symptom Assessment Scale. Similarly, the OH Daily Activity score is calculated as an average of the responses to the four questions on the OH Daily Activity Scale. The overall OHQ score is calculated as an average of the Symptom Assessment score and Daily Activity score (added together and divided by two). Items that are marked as zero or 'cannot be done for other reasons' at baseline are not included in the scoring.

The OHQ is validated for use in both clinical and research settings [26]. The study has been powered to detect a change of 1.0 in the OHQ score (see Section 8.3).

3.4.2 Secondary Outcome Measures and Endpoints

The secondary endpoints will be measured over 12 months from randomisation:

Effectiveness and Safety

- The OHQ will also be measured at baseline, three, six and 12 months post-randomisation to assess the change in OH symptoms.

- The Nottingham Extended ADL scale will be collected at baseline, three, six and 12 months post-randomisation to assess independence in activities of daily living.

  [The Nottingham Extended ADL scale is a validated outcome measure consisting of 22 items over two pages. Each item relates to an everyday activity which is rated according to ability to carry it out (not at all, with help, on your own with difficulty/on your own)].

- EQ-5D-5L collected at baseline, three, six and 12 months post-randomisation to assess impact on health-related quality of life.

  [The EQ-5D-5L general health questionnaire evaluates five domains, which include: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (18). This two-page questionnaire consists of five dimensions, with the responses recorded at five levels of severity (no problems, some problems or extreme problems). The second page consists of a standard vertical 20 cm visual analogue scale which is transformed to a scale of 0 to 100 measuring current health-related quality of life. A proxy version of the EQ-5D-5L will be included for participants who are unable to self-complete the questionnaires].

- QALYS over the 12 months post-randomisation, estimated from response to the EQ-5D-5L using the area under the curve approach.

- Falls data (including number of falls, number of fallers/non-fallers, fall rate per person year, time to first fall, fall-related injuries, number of syncopal events, combined number and rate of falls and syncopal events) will be collected from participants' falls diaries over the 12-month study period.

- Standing nadir BP and postural BP drop will be measured from Lying Standing Blood Pressure (LSBP) collected at baseline, three, six and 12 months. Where follow-up is carried out face-to-face this will be measured according to local practice. If the participant is unable to attend a face-to-face visit (clinic or home visit) and follow-up is conducted remotely, either a postural BP assessment documented in the medical records (in the preceding eight weeks for the eligibility assessment, or the preceding six weeks for the follow-up timepoints), or a self-assessed LSBP may be used. Missing LSBP values and reasons will be closely monitored.

    - To allow for future changes to clinical services (e.g. temporary closure due to COVID-19), an automatic BP monitor will be provided to appropriate participants, alongside an instruction leaflet, to allow them to measure their own LSBP without the need for a hospital visit

- Other important clinical outcomes including hospital admissions, Adverse Events and Adverse Reactions will be collected over the 12-month study period and recorded on the CRF and reported as per protocol.

Economics

- Use of health services over the 12-month follow-up period estimated from the Health and Social Service Use questionnaire collected at baseline (to control for baseline imbalances in use of health services), three, six and 12 months and from the CRF.

  The Health and Social Service Use questionnaire is developed specifically to address the research questions posed in this study. It is informed by the Client Service Receipt Inventory (CSRI), [27] existing health service utilisation questionnaires collated by the MRC funded Database of Instruments for Resource Use Measurement (DIRUM) project (www.dirum.org).

  The Health and Social Service Use questionnaire does not include medications, as the cost of common medication other than the trial medications will be negligible.

- Costs to the NHS, personal social services and patients over 12-month follow-up period estimated from responses to the Health and Social Service Use questionnaire (see above), the time and travel questionnaire completed at six months and from the CRF.

  The Time and Travel questionnaire is developed specifically to address the research questions posed in this study. It is informed by the work of the UK working party on assessing patient costs and resources use questionnaires [28, 29] collated by the MRC funded DIRUM project.

- Incremental cost per QALY gained over the 12-month follow-up period from the perspective of the NHS and personal social services.

Recruitment and Feasibility

- An electronic screening log, integrated in Sealed Envelope, will be used to collect screening data including: the number of patients who meet the eligibility criteria, the number of patients who do not meet the eligibility criteria, and the reasons for ineligibility, and for patients who choose not to participate in the study. The log will be monitored throughout both the 10-month pilot period and the full trial recruitment period. Recruitment procedures, study design and eligibility criteria will be reviewed.

- eCRFs will be used to capture adherence to the treatment allocation and cross-over at each of the data collection time points. Reasons for cross-over and withdrawal from study activity will be collected. This will be monitored throughout the 10-month pilot period and used to assess feasibility of the six-month primary outcome point.

- Use of secondary health care resource will be collected via the eCRF. Use of primary health care and personal social services will be collected by self-administered questionnaires (Health and Social Service Use Questionnaires) at baseline, three, six, and 12 months. Other healthcare resource use (primary care, private care and personal social services) will be collected by self-administered questionnaires at baseline, three, six, and 12 months. Note data in use of health services in the three months prior to randomisation will be collected at baseline. These data will solely be used to adjust for imbalances in resource use prior to randomisation.

- The cost of accessing care by participants and their families will be estimated based on responses to the Time and Travel Cost questionnaire completed at six months.

3.5 Trial Setting and Duration

This multicentre trial will be conducted in approximately 20 NHS trusts across the UK. It is anticipated that participants will be recruited from a number of secondary care settings including but not limited to, falls clinics, day hospitals, geriatric medicine clinics and movement disorder clinics.

During the 10-month pilot phase we intend to open 14 centres. Following the internal pilot an additional six sites will be opened to reach a total randomisation target of 366 patients over the 30-month recruitment period (20 sites in total). Participants will be followed up for a total of 12 months following randomisation.

4. Trial Participants

4.1 Overall Description of Trial Participants

Adults aged 18 years or over with symptomatic OH will be screened for eligibility. Eligibility must be confirmed by a medically qualified doctor using the eligibility confirmation document and documented in the participant's medical notes. Only personnel formally delegated by the Principal Investigator at each site to assess eligibility may perform this task.

4.2 Inclusion Criteria

- Adults aged 18 years and over
- A clinical diagnosis of symptomatic OH which is either:

1. Clinically significant where you would wish to start treatment quickly without a trial of lifestyle modification OR
2. Refractory to an adequate period of lifestyle modification (to be judged clinically)

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

4.3 Exclusion Criteria

- OH secondary to acute or reversible causes (e.g. haemorrhage, sepsis)
- Use of fludrocortisone or midodrine within the last six months
- Terminal illness or life expectancy <12 months
- Supine hypertension (where the risks of treatment outweigh the benefits) at baseline
- A known allergy to study medication
- A known contra-indication to fludrocortisone or midodrine which outweighs the potential clinical benefit (i.e. if in usual clinical care the clinician and participant feel the risks outweigh the benefits, they would be excluded)
- Current or planned pregnancy during the trial period, or breast feeding (if randomised to either pharmacological arm the participant, if female and of child-bearing potential, must have a negative pregnancy test [urine beta-human chorionic gonadotropin (β-hCG)] and are required to use a highly effective contraceptive method during the trial).
- Inability to communicate in English
- Inability to comply with the study procedures as specified in the schedule of events.
- Currently taking part in another clinical trial that would interfere with the outcomes of CONFORM-OH (site team to check with the CI and Trial Management Group if in doubt)

NB: Enrolling a patient onto the trial who does not meet the inclusion/exclusion criteria is considered a protocol waiver and is in breach of Regulation 29 (SI 2004/1031) of the Medicines for Human Use (Clinical Trials) Regulations 2004. PROTOCOL WAIVERS ARE NOT PERMITTED.

5. Trial Procedures

5.1 Recruitment

5.1.1 Pre-screening, Screening and Eligibility Assessment

Adults attending routine clinic appointments (including face-to-face, telephone, video or other forms of consultation) at participating sites, should be pre-screened to confirm they have symptomatic OH requiring treatment. Pre-screening can also include reviewing local patient research participation databases, clinic lists and opportunistic screening. Information about the study may also be displayed on posters in the relevant clinical areas at participating sites so that potential participants will be able to approach staff for more information.

The initial approach will be made by the clinical team. The research team can only approach patients directly if they are imbedded within the clinical team, or permission has been obtained from the patient for them to carry out this activity.

Potential participants identified from pre-screening should be screened for eligibility into the trial using the patients' medical history. All patients screened for eligibility should be recorded on the screening log and assigned a screening identification number, irrespective of their participation in the trial; reasons for ineligibility and non-consent will be captured.

Following eligibility screening, patients that may be eligible will be provided with the Patient information leaflet (PIL) by the clinical team prior to their routine clinical appointment, along with a letter explaining that they may be eligible to take part in a research trial. During the clinical appointment the clinical team will discuss the study and confirm that the patient meets the eligibility criteria for consent.

If for any reason the patient did not receive the PIL in advance of their clinic appointment, the clinical team will inform the patient of the trial, ensure the patient is provided with a PIL, and request the patient's permission for a member of the clinical or research team to contact them to discuss the trial in more detail and answer any questions.

No research activity will take place prior to informed consent.

Re-screening is permitted if deemed necessary by the physician, and must be documented thoroughly and clearly at site, in the patient notes and on the eCRF. If re-screened participants will be given a new screening identification number.

5.1.2 Informed Consent

Potentially eligible patients will be provided with a PIL which will explain the exact nature of the study, the implications and constraints of the protocol and any risks involved in taking part. It will be clearly stated that the patient is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. However, patients will be informed that we would like to know their reason for withdrawal, to assist with the identification of problems with the study and areas to improve. The study will be explained in more detail by a member of the clinical or research team and patients will be given the opportunity to ask any questions. If the research team provides study information, the treating clinician will first obtain permission from the patient for them to carry out this activity.

Patients who received the PIL prior to their clinic appointment, and would like to participate, can have their eligibility confirmed following full consent discussions between the patient and clinician, with consent obtained at the clinic appointment or remotely.

Patients who are provided with the PIL at the clinic appointment, will be given adequate time to consider participation, after which a member of the research team will contact them to provide the opportunity to ask questions and discuss the study. If the patient would like to participate, eligibility can be confirmed using the eligibility confirmation document and an appointment can be arranged for the consent form to be completed using one of the following methods:

1. Completion of the consent process at a routine face-to-face clinic visit, research clinic or home visit.
2. Remote completion of the consent process via videoconference. The consent form is provided in advance and is signed by the participant, witnessed by the consenting clinician using videoconference facilities. Additional identification questions should be asked, in line with local policy to confirm the identity of the patient prior to the consent form being signed.
3. Remote completion of the consent process via telephone. The consent form is provided in advance and is signed by the participant whilst the consenting clinician is present on the telephone. Additional identification questions should be asked, in line with local practice to confirm the identity of the patient prior to the consent form being signed.

If the consent form is completed via videoconference or telephone, the clinician will carry out full consent discussions and answer any questions prior to obtaining agreement from the patient to participate in the study. The clinician will go through each item on the consent form and ask the patient to initial each box, if they agree to consent to the statement, and sign and date the consent form whilst on the call. Consent will be obtained by a suitably-qualified clinician, trained in obtaining consent and delegated that role on the Delegation Log. The patient will be asked to return the signed consent form by post for counter signature by the clinician who obtained consent. The consent form should be received by the clinician who obtained informed consent and counter signed prior to any study-specific activities taking place, this includes randomisation. It is acceptable for a completed consent form to have different dates of signature by the patient and by the person obtaining consent when this is performed remotely.

The participant must personally print their name, sign and date the latest approved version of the Informed Consent Form. In cases where the patient is unable to print their name or date the consent form, for example in cases where patients have Parkinson's disease, this can be completed by another person e.g. a family member, in the presence of the patient at their request. The consent process must be fully documented in the participant's medical notes and in the Event that a participant is assisted to complete the consent form (e.g. to print participant name or date), a file note should be attached to the consent form, detailing that another person has assisted with completion the consent form on behalf of the participant and alongside the reasons why. However, the consent form cannot be signed on behalf of the patient; the patient must always add their own signature.

Participants will be provided with a copy of their fully signed consent form. A copy will be filed in the medical records and a copy sent to the participant's GP along with the PIL. The original signed consent form will be retained at the study site in the Investigator Site File (ISF).

Details of the eligibility assessment and informed consent process should always be documented in the medical records. The original eligibility confirmation document must be signed off by the clinician obtaining informed consent. The original document should be filed in the site file and a copy in the medical records.

A copy of the completed consent form and eligibility confirmation document will also be sent by site to the secure NCTU email (nctu.conform-oh.conf@nhs.net) – this is for safety monitoring purposes. An nhs.net account must be used to send these documents. For sites that do not have nhs.net accounts, another secure method may be used but this must be discussed with and agreed by the NCTU Trial Manager(s) prior to use.

5.2 Baseline Assessments

The participant's completed consent form must have been received at site and counter-signed by the clinician obtaining remote informed consent before this visit and collection of self-reported assessments can take place. Preference is given to face-to-face appointments, but these can be completed remotely if required. Baseline assessment consists of the Orthostatic Hypotension Questionnaire (OHQ), the EQ-5D-5L or its proxy version [30] and the Nottingham Extended ADL Scale. Also completed will be the Health and Social Service Use questionnaire. Contact details and demographic data including age, sex, ethnicity, height and weight (self-report is acceptable if the assessment is carried out remotely), co-existing medical conditions and culprit medications will be collected.

Supine and nadir standing BP will also be collected at baseline and should be obtained during using one of the methods in section 5.4.1.

In participants with known Parkinson's disease, Dementia with Lewy bodies or Multiple System Atrophy the severity of their motor symptoms will be quantified with parts 1, 2 and 4 of the Movement Disorder Society's Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Online training will be provided to researchers who are unfamiliar with this tool. See Schedule of Events (Section 5.6) for more details.

To be eligible to be randomised, the participant will be required to meet ALL of the inclusion criteria and NONE of the exclusion criteria at this time point (see Section 4)

At all time-points, if participants have remote trial appointments, questionnaires can be posted to them at home, for completion and return to the site.

At the Baseline/Randomisation appointment, participants will be provided with a falls diary to complete at home and requested to bring or post the falls diary prior to/following each follow-up visit.

5.3 Randomisation

Consented participants who meet the eligibility criteria in Section 4 will be randomised on a 1:1:1 ratio to:

I. Control: Conservative management
II. Conservative management plus fludrocortisone
III. Conservative management plus midodrine

Randomisation will be performed by delegated and trained members of the research team at each site using a 24-hour, central, secure, web-based system (Sealed Envelope™). In the event that there are problems with randomisation, the team should contact the NCTU Data Management team during normal working hours who will be able to provide advice. In the event that Sealed Envelope is not available at site due to a technical fault, the team should contact the NCTU who will liaise with Sealed Envelope Support to investigate the cause.

A minimisation algorithm with a random element will be used to assign treatment allocation. Minimisation factors will be by age (≥80 or <80 years), aetiology (neurogenic vs non-neurogenic) and centre (for possible differences in usual care practice). There is an 80% chance the patient is allocated to an arm that minimises imbalance, with 20% chance they are allocated to a different arm.

Participants will be informed of their treatment allocation and the clinical team will provide the advice and relevant medications as per routine practice at the site. IMP should be started as soon as possible. For women of child bearing potential who are randomised to either pharmacological arm of the study, a negative pregnancy test will be required prior to commencing the medication. As part of usual care, a safety blood test will be carried out to monitor urea and electrolytes (both drug arms), and liver function (midodrine arm only). These are safety bloods only and should take place within three months of initiation of the IMP and every six months thereafter. Results will not be recorded for the purpose of the research, unless required for safety reporting in the event of an Adverse Event.

5.3.1 Masking

This is an open-label, unblinded trial. Study participants, clinicians and the NCTU team will be aware of treatment allocation. The Statistical Analysis Plan (SAP) will be developed by statisticians who are unaware of treatment allocation and will be finalised and signed-off prior to the first DMC meeting that reviews unblinded data. The SAP will contain full details of both the interim and final analyses, with details of who will perform these analyses. Trial statisticians will have access to unblinded data for the purposes of creating DMC reports and conducting the interim analysis. No other members of the research team will have access to the unblinded data contained in closed DMC reports, unless the DMC request that unblinded information is released. In the case that an amendment is proposed to the SAP, this will be approved by an appropriate blinded independent statistician (the independent Trial Steering Committee statistician or an appropriate senior member of the Biostatistics Research Group).

5.4 Follow-up assessment time points

Follow-up visits should align with local routine clinical pathway where possible.

Consultations can be conducted at face-to-face appointments; however, remote methods can be used according to usual local practice, if face-to-face is not possible. Consultations can be completed by Research Nurses and specialist Nurses but the clinician must retain clinical oversight and responsibility.

5.4.1 Blood Pressure monitoring

Supine and nadir standing BP is measured at multiple time points throughout the study and should be obtained using one of the following options:

1. LSBP measured during a face-to-face appointment
2. LSBP which is documented in the medical records and has been measured within the preceding six weeks of the follow-up visits or within the previous eight weeks of the eligibility assessment; the BP measurements used for eligibility can also be used as baseline BP measurements

3. Self- assessed LSBP measured at home using own BP machine or a BP machine provided by the study

If a participant has a previous diagnosis of OH but their last BP measurement was not taken in the 8 weeks preceding consent the baseline BP can be used to assess eligibility. This must be obtained after consent but prior to confirm the participants eligibility for the trial.

5.4.2 Follow-up Visits (Three, six and 12 Months)

The clinical/ research team will schedule the three-, six- and 12-month follow-up clinic appointments with all participants. These should be face-to-face, if possible; however, remote follow-up visits are acceptable. This is a pragmatic study so some variability in the timing of follow-up assessments is acceptable (see schedule of Events for follow-up windows).

All participants will have their supine and nadir standing BP taken or provide self-recorded BP measurements if follow-up is remote (acceptable methods for obtaining BP measurements are listed in Section 5.5.1).

Blood tests will be carried out/arranged as part of their usual clinical care (see Schedule of Events).

At the three-month follow-up participants who were randomised to receive IMP will be asked to confirm that they have started the prescribed IMP.

Participants will be asked to either provide their falls diary at each follow-up visit or provide details from their falls diary over the phone when they speak to the site research team member or clinician. At each consultation, participants will be reminded to complete their falls diary and bring it with them to their next face-to-face follow-up visit or have it to hand to allow the information to be provided over the phone/video call. If participants forget to bring their falls diaries to their face-to-face consultation or are unable to attend face-to-face consultations this data can be collected over the phone and a new diary can be posted out with a self-addressed envelope for return of the partially completed diary to enable timely data collection.

Participants will be required to complete the OHQ, EQ-5D-5L, Nottingham Extended ADL Scale and the Health and Social Service Use questionnaire. Additionally, participants will complete a Time and Travel Questionnaire at the six-month follow-up consultation. For remote visits, these questionnaires will be completed by the clinician over the phone/videoconference with the participant.

Data regarding adherence to trial intervention, culprit medications and Adverse Events will be collected and recorded in the CRF.

For sites who carry out face-to-face follow-up with patients in the community as routine practice, these consultations can be scheduled at the participant's home. However, a medically qualified, GMC registered clinician must retain oversight.

5.4.3 Non-study Visits

Clinicians may review participants as part of routine clinical care between these time points for dose titration or other clinical reasons. These consultations will be recorded in the participant's medical notes and the eCRF, including details of medication changes and AE/SAE details if applicable.

5.5 Schedule of Events

	Routine Clinical assessment	Consent contact	Clinical review	Clinical review	Clinical review	Clinical review
			Baseline Week 0	Three months	Six months Primary Endpoint	12 months
Follow-up Window	Consent, baseline and randomisation can take place at one visit if the patient receives the PIL in advance			+/- 4 weeks	+/- 6 weeks	+/- 8 weeks
Eligibility Screening	x		x			
Confirm provisional eligibility	x		x			
First approach (treating clinician)	x					
Provide PIL (RN or clinician)	x					
Written informed consent[a]	x	x				
Baseline data collection						
Demographics (DoB, gender, ethnicity) and medical history (including disease duration if PD/MSA/DLB)			x			
MDS-UPDRS parts 1, 2 and 4 (PD / MSA/DLB patients only)			x			
Height and weight			x			
Outcome measures						
Supine and standing BP[b]	x		x	x	x	x
OHQ[c]	x		x	x	x	x
EQ-5D-5L			x	x	x	x
Nottingham Extended ADLs			x	x	x	x
Health and Social Service Use Questionnaire(s)			x	x	x	x
Time and Travel Questionnaire					x	
Randomisation						
Confirm eligibility for randomisation			x			
Randomisation via Sealed Envelope			x			
Routine non pharmacological management – may vary at different sites but might include;						
Lifestyle advice may include: • trigger avoidance • slow, staged, safe standing • salt intake • hydration • bolus water drinking • caffeine intake • education of condition	x		x	x	x	x
Provide compression garments (if usual clinical practice)	x		x	x	x	x

Physical counter-manoeuvres (if usual clinical practice)	x		x	x	x	x
Abdominal compression (if usual clinical practice)	x		x	x	x	x
Culprit medication review	x		x	x	x	x
Participants randomised to IMP						
Pregnancy test[d]			x			
Instruction regarding IMP and local prescription arrangements[e]			x	x	x	x
Drug safety monitoring urea & electrolytes as per local practice (drug arms only)[f]			x	x	x	x
Liver function tests (midodrine arm only) as per local practice[f]			x	x	x	x
Confirmation that participant is taking IMP				x	x	x
Additional outcome measures – for all participants						
Provide participant with falls diary			x	x	x	
Falls diary review				x	x	x
Adverse Events review (including hospital admissions)				x	x	x

[a] Consent should be obtained at a face-to-face clinic. If this is not possible it can be obtained via videoconference or telephone. Consent only needs to be obtained once (at routine clinical assessment or the consent contact)

[b] If lying and standing blood pressure were measured at the routine clinical assessment they do not need to be repeated at Baseline. For eligibility, BP measurement can be carried out at baseline following consent, or in the preceding eight weeks, or for follow-up visits the preceding six weeks.

[c] OHQ to be carried out prior to consent if part of usual care at local site

[d] A urine sample pregnancy test for all female participants of child-bearing potential randomised to either intervention arm

[e] Fludrocortisone and midodrine will be prescribed and provided according to local clinical practice

[f] U&Es and liver function tests to be carried out as per routine practice of treating clinician but at a minimum within three months of initiation of the IMP and every six months thereafter. These will not be reported for research purposes

5.6 Discontinuation of Participants from Allocated Study Treatment

Participants have the right to discontinue the allocated trial treatment at any time. The participant is not required to provide a reason; however, they will be encouraged to do so to ensure that information relevant to the study design, intervention tolerability and efficacy is collected where possible.

In addition the investigator or the treating clinician may discontinue a participant's allocated treatment from the study if deemed necessary for any reason which may include pregnancy, intolerable side effects, or lack of efficacy. The investigator will be encouraged to discuss these cases with the CI and document the reasons for treatment discontinuation.

Where possible participants and investigators will be encouraged to continue on the allocated treatment until the primary outcome point at six months, as long as this does not put participants at risk.

Participants will not be withdrawn from the trial if treatment contamination, cross-over or treatment discontinuation occurs, but will remain in the trial and be offered all follow-up data collection visits as part of the intention-to-treat analysis. If allocated study treatment changes during the trial, details of the changes, including when, by whom and why the decision was made should be made in the CRF.

5.6.1 Supine Hypertension

The decision to discontinue study medication because of supine hypertension lies with the site PI. No threshold for discontinuation is stipulated, as the balance of risk and benefit will differ from participant to participant, but a supine systolic BP of <160 should not usually lead to discontinuation of medication [31]. A diagnosis of supine hypertension should not be based on a supine BP measured within four to six hours of a midodrine dose.

Although supine hypertension may increase the risk of cardiovascular events, some individuals may be willing to accept the risk if their symptoms of OH outweigh the risk. This is particularly true for those who have profound drops in BP, where a higher supine BP may be required to achieve higher standing BPs.

Home monitoring, ideally with an automated 24 hour BP monitor, is best practice if feasible. Dose reduction of fludrocortisone or midodrine may improve supine hypertension. An alternative strategy is the encouragement of head-up posture during recumbency, by elevating the head of the bed.

5.7 Withdrawal from the Study

Participants who withdraw once they have been randomised will not be replaced. Any reason for withdrawal will be recorded in the CRF and participant's medical notes.

Where participants state they want to withdraw from the study, sites should try to ascertain the reason for withdrawal and document this within the CRF and participant's medical notes.

If a participant does not want to attend any further study follow-up consultations but is willing to carry out questionnaires over the phone or by post they may continue in the study. This is not a withdrawal of consent and routinely collected data such as clinical postural BP can be collected from the medical records and documented in the CRF.

Where a participant decides to withdraw their consent and does not wish to participate in any further research activity they will asked to choose from the following withdrawal options:

1. Withdraw from further research activity but allow the use of data collected up to the point of withdrawal and any future routinely collected data from medical records where relevant to the outcomes of the study.

2. Withdraw from further research activity and allow the use of data collected up to the point of withdrawal but does not allow the use of any routinely collected data from the point of withdrawal.

In all cases, data collected up to the point of withdrawal will be retained and included in the analysis unless the participant specifically requests the removal of this data. Unless a participant declines the collection of routine data from medical records after they have withdrawn from the study, at 12 months sites will obtain data on blood pressure recordings, hospital admissions, procedures/operations and outpatient visits that have occurred in the duration of the study.

If the participant loses capacity they will be withdrawn from the study. However, if the investigator judges the loss of capacity to be reversible and short-term (e.g. acute delirium) and appropriate, the participant will continue in the study. This situation will be assessed on a case-by-case basis.

The occurrence of an Adverse Event is not a reason to withdraw a patient from the study.

5.8 Protocol Deviation, Protocol Breach or Non-compliance

Protocol deviation, protocol breach or non-compliance with trial medication or study processes will not lead to withdrawal of the participant from the trial, even if it is necessary to discontinue study medication as a result of such a breach. If a participant wishes to withdraw from study medication or change to a different treatment strategy, they will be encouraged to continue with the study follow-up assessments. Participants who have their allocated treatment stopped or modified (e.g. due to intolerable side effects) will continue in the trial to preserve the intention-to-treat analysis, this includes participants whose medication is changed for clinical reasons. This will be documented clearly in reporting and analysis.

5.9 Definition of End of Trial

The end of the clinical trial is defined as the final participant's 12-month follow-up visit. All data queries will be resolved, as far as possible, before the database is locked. The Sponsor, CI and the TSC have the right at any time to terminate the trial for clinical or administrative reasons.

The end of the trial will be reported to the Sponsor, Research Ethics Committee (REC), Regulatory Authority (RA) and NHS R&D Office(s) within 90 days, or 15 days if the study is terminated

prematurely. It is the CI's responsibility to ensure that any appropriate follow-up is arranged for all participants; this will be delegated to the site PIs.

A final report will be provided to the Sponsor, REC, MHRA and Funder within one year of the end of the study.

6 Trial Intervention

Participants will be randomised to one of three interventions:

I. Conservative management only (non-pharmacologic treatments)
II. Conservative management plus fludrocortisone
III. Conservative management plus midodrine

6.1 Description of Conservative Management

For the purpose of this study, non-pharmacologic therapy is referred to as conservative management. Conservative management is standard first-line care and forms the control arm of this trial.

Conservative management may consist of the following:

- Education about the condition
- Trigger avoidance (avoiding dehydration, alcohol, excess caffeine, large meals, hot environments, aerobic exercise and specific personal triggers)
- Safe standing (using the skeletal muscle pump before standing, moving slowly to an upright position, particularly in the morning and the use of counter-manoeuvres during standing)
- Physical counter-manoeuvres (these are adapted to an individual's ability and include standing with legs crossed, repeated calf raises and knee bends, tensing legs, abdominals and buttocks. Some sites may use biofeedback to demonstrate the efficacy of these manoeuvres during BP monitoring. Study sites will continue to perform their usual clinical practice)
- Fluid and salt intake (avoid dehydration, bolus-water drinking, at least 10 g (two teaspoons) of salt per day)
- Compression hosiery (Grade 2 full leg length compression stockings and/or abdominal binder)

The specific conduct of conservative management will vary between sites. Conservative management will begin following diagnosis, as is usual clinical practice.

6.2 Name and Description of IMP

For the purposes of this trial fludrocortisone and midodrine will be classed as IMP.

Fludrocortisone – currently used outside of licenced indication, but according to clinical guidelines and the BNF dosage schedule. The BNF recommends a dose range of 100 to 400 micrograms daily. In line with current clinical practice this study will include the option of a lower starting dose of 50 micrograms, which can be used for participants who are judged by the PI to be frailer and appropriate for this lower dose; any brand of fludrocortisone may be used.

Midodrine – licensed for severe OH due to autonomic dysfunction when corrective factors have been ruled out and other forms of treatment are inadequate. The recommended dose range is 2.5 mg three times a day to 10 mg three times a day. Lower frequency doses (e.g. 2.5 mg twice a day) are acceptable within this study as judged by the local clinical team; any brand of midodrine may be used.

6.3 Reference Safety Information (RSI)

For the purposes of this study the following comprehensive SmPCs will be used for the Reference Safety Information (RSI).

The RSI for fludrocortisone acetate 0.1 mg tablets can be found in Section 4.8 "Undesirable effects" of the currently approved version of the SmPC.

The RSI for midodrine (for the purpose of this study all midodrine brands will be referenced against the SmPC for Bramox 2.5 mg tablets as this is the only brand of midodrine at the time of study approvals) can be found in Section 4.8 "Undesirable effects" of the currently approved version of the SmPC.

Serious Adverse Reactions (SARs) that are thought to have a causal relationship to fludrocortisone or midodrine must be assessed for expectedness against the RSI outlined above only.

In the event of a SAR that is thought to have occurred due to a reaction between the IMP and other medicinal products, please also ensure to check Section 4.5 of the SmPCs for fludrocortisone and midodrine (Bramox) 'interaction with other medicinal products and other forms of interaction'.

6.4 Drug Storage and Supply

IMP will be provided, open label, by local clinical teams according to their usual prescribing practices. No specific storage instructions arise as a result of this study and no temperature monitoring or accountability of the products is required to be carried out by sites. Storage should be in line with the product SmPC being utilised for the treatment.

6.5 Preparation and Labelling of IMP

Labels and packaging will follow local usual clinical and dispensing practices, which may differ between sites. Annex 13 compliant labelling is not required on the products at the point of dispensing.

6.6 Dosage Schedule & Modifications

6.6.1 Fludrocortisone

Usual local clinical practice will be followed. A typical starting dose 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. 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. However, it is accepted that this may not always be possible. The maximum allowed dose within this study is 400 micrograms as stated in the BNF, however we anticipate most sites will use a maximal

dose of 300 micrograms as this is usual practice. It is acceptable to reduce the dose in the presence of side effects or Adverse Events if the clinician would do this as part of their usual clinical practice.

6.6.2 Midodrine

Usual local practice will be followed. The typical starting dose will be 2.5 mg TDS 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. However, it is accepted that this may not always be possible. The maximum dose within this study is 10 mg TDS. Although higher doses are rarely used (e.g. 15 mg TDS), they will not be allowable within this study. It is acceptable to reduce the dose in the presence of side effects or Adverse Events if the clinician would do this as part of their usual clinical practice.

6.7 Known Drug Reactions and Interactions

For a full list of side effects and safety information refer to the relevant SmPC.

6.8 Concomitant Medications

It is anticipated that the majority of participants will be taking multiple medications. There are no absolute contra-indications to other medications. Local research teams should follow their usual clinical practice and consult the BNF to review cautions and contra-indications. In line with clinical guidelines, clinicians will be required to review those medications known as 'culprit medications'. These could cause or worsen OH, and are as follows: alpha-blockers, beta-blockers, Calcium channel blockers, diuretics, ACE-inhibitors, Angiotensin II Receptor blockers, Nitrates (regular, not PRN), other vasodilators (eg sildenafil, nicorandil), other anti-hypertensives (eg clonidine), tricyclic anti-depressants, dopamine agonists, SSRI anti-depressants, anti-psychotics, Levodopa, Monoamine oxidase inhibitors (MAOI), and catechol-o-methyltransferase (COMT) inhibitors [1, 17, 32]. Other current treatments for OH that should be checked for at each visit are atomoxetine, pyridostigmine, octreotide and desmopressin A risk/benefit decision will be made by the participant and clinician (as would be usual clinical practice), whether to discontinue, modify or continue any of these medications. Given the pragmatic nature of the trial, participants may still enter the study if they continue 'culprit' medication(s); Culprit medications should be reviewed at each trial visit and document any changes in the participants medical record and eCRF.

6.9 Assessment of Compliance

As a pragmatic study of clinical effectiveness of current care pathways, participants' adherence to prescribed medication and non-drug therapies will not be monitored.

6.9.1 Cross-over and Treatment Withdrawal

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 we will not seek to dictate clinical decisions, we ask the clinical teams 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.

If allocated study treatment changes during the trial, details of the changes, including when, by whom and why the decision was made should be recorded in the eCRF.

Participants will not be withdrawn from the trial if treatment contamination, cross-over or withdrawal occurs, but will remain in the trial and be offered all follow-up data collection visits as part of the intention-to-treat analysis.

7 PHARMACOVIGILANCE

7.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward or unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as Adverse Reactions
Reference Safety Information (RSI)	The RSI is a list of medical terms detailing the ARs that are expected for an IMP and must be referred to when assessing a SAR for expectedness.
Serious Adverse Event (SAE)	A serious Adverse Event is any untoward medical occurrence that: • Results in death • Is life-threatening* • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity • Consists of a congenital anomaly or birth defect • Other important medical events that jeopardise the participant or require intervention to prevent one of the above consequences * Life-threatening refers to an event in which the participant was at immediate risk of death at the time of the event; it does not refer to

	an event which hypothetically might have caused death if it were more severe
Serious Adverse Reaction (SAR)	An Adverse Event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based upon the information provided
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious Adverse Reaction, the nature and severity of which is not consistent with the approved Reference Safety Information

7.2 Recording Adverse Events and Adverse Reactions (AEs and ARs)

All AEs and ARs will be recorded from the date of randomisation until completion of 12-month visit or until the participant withdraws. Participants will be asked about AEs and ARs at each scheduled study visit.

All AEs and ARs (unless listed below in 7.3) will be recorded in the participants' medical notes and the data entered onto the AE page in the electronic case report form (eCRF). The local site PI's clinical judgement should be used to determine if an AE is reportable as an AR.

7.3 Exclusions to Adverse Event (AE) reporting

Due to the nature of the study design the following AEs are exempt from recording unless the PI deems them to be related or serious;

- Falls -these are captured as an outcome. However, any injury resulting from a fall will be recorded as an Adverse Event.
- The following symptoms are routinely experienced in people with OH and therefore will not be reported as AEs:
    - Dizziness/light-headedness/vertigo
    - Postural induced visual disturbance
    - Weakness/fatigue/tiredness
    - Difficulty concentrating
    - Headache or head/shoulder/neck discomfort
    - Tremulousness
    - Pallor
    - Anxiety
    - Palpitations
    - Nausea

7.4 Assessment of Adverse Events/ Adverse Reactions (AEs/ARs)

AEs/ARs will be recorded at study visits by the research team. AEs/ARs will be recorded on the paper AE log, transcribed into the eCRF and in the patient medical notes. Each AE/AR must be assessed for severity (7.4.1), seriousness (7.4.2) and causality (7.4.3).

7.4.1 Assessment of Severity

Each AE/AR must be assessed for severity by the PI/delegated clinician. The following definitions should be used:

Intensity	Description
Mild	An event tolerated by the patient, causing minimal discomfort and not interfering with everyday activities
Moderate	An event sufficiently discomforting to interfere with normal everyday activities
Severe	An event that prevents normal everyday activities

7.4.2 Assessment of Seriousness

The PI/delegated clinician must make an assessment against the standard definition in the Safety Reporting Definitions (Section 7.1).

7.4.3 Assessment of Causality

All AEs/ARs occurring from the time the participant is randomised into the study until the participant's 12-month study visit or participant withdraws, must be assessed for the relationship to the study intervention by the PI/delegated clinician. Due to the low risk nature of the study intervention, any AE classified as 'unrelated' or 'unlikely to be related' will be deemed unrelated for the purpose of reporting SUSARs. If there is any doubt, the CI may be consulted. If the PI and CI assessment differ then both assessments will be reported. The following definitions should be used:

Unrelated	The event is not considered related to the study interventions.	Unrelated
Unlikely to be related	There is little evidence that the trial intervention caused the event. There is another more likely explanation.	
Possibly related	There is some evidence that the trial intervention may have caused the event. Other causal factors cannot be ruled out.	Related
Probably related	The temporal relationship and an absence of a more likely explanation suggest that the study intervention is the most likely cause.	

Definitely related	The known effects of the study intervention indicate that it is the most likely cause; other contributing factors can be ruled out.	

7.5 Reporting of Serious Adverse Events and Serious Adverse Reactions (SAEs and SARs)

All Adverse Events and Adverse Reactions occurring from point of randomisation until the participants' final study visit that meet the definition of serious (as outlined in Section 7.4.1 above) will be regarded as a Serious Adverse Event or Serious Adverse Reaction. These will need to be reported to NCTU as part of this trial and recorded in the eCRF and patient medical records. All corresponding AEs will be recorded on the eCRF and marked as serious. SAEs must be followed up until resolved.

All SAEs and SARs not listed in Section 7.7, will be reported to the CI, NCTU and Sponsor as soon as possible within a maximum of 24 hours of the site becoming aware of the event.
The initial SAE or SAR report will be made by the site PI (or delegate) completing the CONFORM-OH SAE reporting form. This can be sent by email to **nctu.Conform-OH.sae@nhs.net** which is automatically distributed to the Senior Trial Manager, Trial Manager, Clinical Trials Assistant, NCTU QA, CI and nominated Sponsor contact. For sites that do not have nhs.net accounts, another secure method may be used but this must be discussed with and agreed by the NCTU Trial Manager(s) prior to use. The initial report can, if necessary, be made to the Clinical Trials Unit by telephone or e-mail and followed up formally using the SAE reporting form.

For each immediately reportable SAE the following information will be collected:

- Full details in medical terms and case description
- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Causality in the opinion of the investigator
- Whether the event is considered expected or unexpected in accordance with the approved RSI if a causal relationship is suspected with study medication

A copy of the completed SAE reporting form will be filed in the ISF as well as in the patient's medical records.

Any change of condition or additional follow-up information should be submitted to NCTU as soon as it is available or at least within 24 hours of the information becoming available. The CONFORM-OH SAE follow-up form should be used for this. Events will be followed up until the event has resolved or a final outcome has been reached.

NCTU contact details:

When reporting SAEs/SARs/SUSARs please send the completed and signed SAE reporting form(s) to the following from a secure nhs.net email address:

Email: nctu.Conform-OH.sae@nhs.net

FAO CONFORM-OH TRIAL MANAGER

A participant should not be withdrawn if they experience an SAE. However, if a participant is withdrawn from the study, the site team will continue to follow up the event until the SAE has resolved or stabilised.

7.6 Assessment of Expectedness

All SARs (SAEs determined as having a reasonable suspected causal relationship to fludrocortisone or midodrine) must be assessed for expectedness.

The assessment of expectedness will be performed by the CI, or delegated to a senior co-investigator in their absence, using the MHRA-approved RSI for the trial (see Section 6.2).

In the event of a SAR, which is thought to have occurred due to a reaction of another medicinal product with the IMP, please also ensure to check Section 4.5 'interaction with other medicinal products and other forms of interaction', of the SmPC detailed in Section 7.8 to assess relatedness. All AEs, and SAEs, unless exempt from reporting (see Section 7.3 and 7.7), occurring from point of randomisation to end of study participation must be recorded in the eCRF as well as the participant's medical notes.

7.7 Protocol Specific SAE Reporting Exclusions

Due to the large amount of comorbid disease, very high levels of illness and Adverse Events that we expect to be present in this population, the following SAEs will be recorded on the AE log within the eCRF, but not reported immediately to NCTU, and not reported using the SAE form:

- Any death or hospitalisation due to new cardiovascular event
- Any death or hospitalisation due to new diagnosis or treatment of cancer
- Any death or hospitalisation due to fall or fracture
- Any death or hospitalisation due to infection
- Any death or hospitalisation due to delirium
- Any hospitalisation due to reduced mobility
- Any death or hospitalisation due to exacerbation of an existing medical condition
- Any admission for elective or planned investigation or treatment
- Any hospitalisation due to nausea, vomiting, constipation or diarrhoea
- Any falls related soft tissue injury, which require medical attention

- Note that the above exceptions to immediate SAE reporting refer only to SAEs where the study medication is not deemed to be causally related to the event by the local PI. Where study medication is deemed to be causally related (SAR or SUSAR) by the local PI, immediate reporting of the event should proceed to NCTU using the CONFORM-OH SAE form.

7.8 Expected Adverse Reactions

Please review the relevant SmPCs for each IMP for a full list of expected reactions and additional details including frequency:

- Fludrocortisone acetate 0.1 mg tablets
- Bramox 2.5 mg tablets

All three-, six- and 12-month ARs to study IMP must be recorded/reported as part of this trial (see protocol Sections 7.2 and 7.6 for AR and SAR recording and reporting details).

Adverse Reactions should be deemed 'unexpected' if the nature or severity of the event is not consistent with the approved RSI which is Section 4.8 of the relevant Summary of Product Characteristics (see protocol Section 6.2).

7.9 Recording and Reporting SUSARs

All SUSARs or suspected SUSARs that occur during this study must be reported by site to the NCTU immediately (and no later than 24 hours of the site becoming aware of the event), through the provided SAE reporting method (see Section 7.5). This will automatically be distributed to the Sponsor and CI.

The assessment of expectedness will be performed by the CI, (or a medically qualified individual delegated this task via the Delegation Log, in their absence) against the approved RSI for the trial. The RSI is contained within Section 4.8 of SmPC:

- Fludrocortisone acetate 0.1 mg tablets
- Bramox 2.5 mg tablets*

* For the purpose of this study all midodrine brands will be referenced against the SmPC for Bramox 2.5 mg tablets.

All SUSARs must be reported to the MHRA and REC. Reporting to MHRA and REC will be performed by the study Sponsor. This is reported using the electronic SUSAR form via the eSUSAR website. A copy of the electronic form and the CTIMP safety report will be sent to the REC in line with Sponsor SOPs.

SUSARs which are determined as fatal and life-threatening must be sent to the MHRA within seven calendar days of notification (with a further eight days for follow-up information) by the Sponsor.

Non-life threatening SUSARs must be reported to the MHRA by the Sponsor no later than 15 calendar days with any relevant follow-up information sought and reported as soon as possible after the initial report.

NCTU will be responsible for ensuring that the CI reviews the expectedness assessment to determine if a SAR is unexpected and requires reporting as a SUSAR. The reporting timeframe starts at day zero when the Sponsor is in receipt of a minimum set of information:

- Sponsor trial reference and trial name (sponsor reference)
- EudraCT number
- Patient trial number and date of birth
- Name of IMP(s)
- Date of notification of the event
- Medical description of the event
- Date and time of the onset of the event (including event end date if applicable)
- Causality assessment
- Seriousness of the event, particularly if life threatening or fatal
- An identifiable reporter (e.g. Principal Investigator)

Sites must report the SUSAR/suspected SUSAR using the CONFORM-OH SAE Reporting Form. This form should be emailed to the trial SAE email address: nctu.Conform-OH.sae@nhs.net (from a NHS.NET email account) which will then be automatically distributed to the trial management team, CI and nominated Sponsor contact. For sites that do not have nhs.net accounts, another secure method may be used but this must be discussed with and agreed by the NCTU Trial Manager(s) prior to use.

The site is expected to co-operate fully with NCTU and Sponsor staff, to ensure that a full and detailed report is submitted to the MHRA and REC within the required timelines.

Site PIs will be informed of all SUSARs reported for the study by NCTU.

7.10 Responsibilities

7.10.1 Principal Investigator

- Checking for AEs and ARs when participants attend for treatment or follow-up
- Using medical judgement in assigning seriousness and causality and providing an opinion on expectedness of events using the RSI version approved for the trial.
- Ensuring that all SAEs and SARs, including SUSARs, are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
- Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

7.10.2 Chief Investigator

- Clinical oversight of the safety of trial participants, including an ongoing review of the risk/benefit.
- Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
- Using medical judgement in assigning expectedness to SARs in line with the RSI.
- Immediate review of all SUSARs.
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol.

- Review/assignment of Medical Dictionary for Regulatory Activities (MedDRA) or body system coding for all SAEs and SARs.
- Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

7.10.3 Sponsor

- Data collection and verification of AEs, ARs, SAEs, SARs and SUSARs onto a database (delegated to NCTU).
- Reporting safety information to the independent oversight committees for the ongoing assessment of the risk/benefit ratio throughout the life of the trial (delegated to NCTU).
- Assessment of expectedness of any SUSARs (delegated to the CI).
- Expedited reporting of SUSARs to the Competent Authority (CA) and REC within required timelines.
- Notification of all investigator sites of any SUSAR that occurs (may be delegated to NCTU).
- Reviewing RSI at least annually and notification of PIs of any required updates (delegated to NCTU).
- Preparing tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC (delegated to NCTU).

7.10.4 DMC

- Review of safety data collected to date to identify any trends.
- Make recommendations to the TSC on study conduct based on any findings from review of safety data.

7.10.5 TSC

- Act on recommendations from the DMC in relation to any safety issues identified in the TSC charter.

7.11 Notification of Deaths

Fatal SUSARs will be reported within seven days to Sponsor, REC and MHRA. Monitoring of all other deaths will occur via the TMG and the DMC.

7.12 Contraception and Pregnancy

The effect of midodrine on pregnancy has not been investigated in humans therefore the advice in the SmPC is that it is not recommended during pregnancy and in women of childbearing potential not using contraception. The SmPC for fludrocortisone indicates risks to the foetus when taken during pregnancy.

Pregnancy, lack of agreement by females to use effective contraception and lactation are all exclusion criteria and the PIL will advise females to contact the local trial team immediately should they become pregnant during the trial.

Highly effective methods of contraception include:

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- intrauterine device (IUD)

- intrauterine hormone-releasing system (IUS)
- vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success)
- bilateral tubal occlusion
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject).

7.13 Pregnancy Reporting

In the event of a study participant becoming pregnant during the study, the site must use a study-specific pregnancy reporting form to notify NCTU, the Chief Investigator and the Sponsor Representative within 24 hours of becoming aware of the pregnancy.

If a participant becomes pregnant, sites should follow routine practice. The participant should be completely withdrawn from the study and referred to the relevant team. Sites should approach the study participant to obtain consent to record the outcome of the pregnancy.

Pregnancy does not constitute a SAE but study participants that become pregnant must be followed up until at least the culmination of the pregnancy to determine if a congenital anomaly or birth defect has occurred. Only congenital anomalies or birth defects are reported as an SAE.

7.14 Overdose

Research teams should consult the SmPC for advice on the management of overdose.

In the event of reported minor overdose (three times usual dose), participants will be assessed by the research team by telephone, at home, GP surgery or local research unit, whichever is the more convenient. They will be given verbal instructions when seen by the research nurse to contact him/her should this occur. If clinically stable, they will be asked to stay at home for that day and avoid any further doses that day. If the participant is unwell, has taken a larger overdose or significant hypertension has been noted as a consequence of the overdose, the RN will refer them to their GP or else directly to A&E for admission and monitoring.

7.15 Reporting Urgent Safety Measures

An Urgent Safety Measure (USM) is an action that the Sponsor or an Investigator may take in order to protect the subjects of a trial against any immediate hazard to their health or safety. Upon implementation of an USM by an Investigator, the NCTU must be notified immediately and details of the USM given. The Sponsor must inform the MHRA and the NHS REC within three days of the USM taking place in accordance with the Sponsor's SOPs.

7.16 Development Safety Update Report (DSUR)

In the UK, a DSUR will be submitted to the MHRA and NHS REC once a year on the anniversary of the Clinical Trial Authorisation date. NCTU must ensure that the report is submitted within 60 days of the end of the reporting period. The Trial Management Group must contribute to the compilation of the DSUR and the CI must review and authorise the final report before it is ready for submission. The DSUR

should also be reviewed by the NCTU QA Manager and Sponsor Representative prior to submission. NCTU staff will prepare and submit DSURs for the trial, in accordance with NCTU SOPs.

8 STATISTICAL CONSIDERATIONS

8.1 Analysis Populations

The following analysis populations will be defined:

Analysis population	Definition
Efficacy Analysis Population 1 - Intention-to-treat (ITT)	• Participants will be analysed according to their randomised treatment group, i.e. following the ITT principle • All available outcome data will be included in the analysis
Efficacy Analysis Population 2	• Participants will be analysed according to their randomised treatment group • Outcome data following cross-over to another treatment group, or discontinuation of allocated treatment, will be set to missing
Safety population	• For each treatment group, all participants exposed will be included in the safety population • Safety data will be summarised according to the treatment strategy received at the time of onset of each AE

The primary outcome will be analysed in the intention-to-treat population with sensitivity analyses in the per-protocol population. Secondary outcomes will be analysed in the intention-to-treat population. Safety data will be reported in the safety population.

8.2 Statistical Analyses

The analysis will follow a fully detailed pre-specified SAP that is approved by the trial oversight committees. This SAP will be finalised prior to the first DMC review of unblinded data.

8.2.1 Analysis of the Primary Outcome Measure

The primary analysis will be a linear mixed-effects model fitted to OHQ at three and six months after baseline. Fixed effects will include treatment assignment, baseline OHQ, baseline age (>=80 or <80 years) and aetiology (neurogenic vs non-neurogenic). A separate treatment assignment parameter will be included for each follow-up time. Random effects will include site and individual (as nested within site). From this model we will use the Wald test of each level of treatment assignment against control (reference) to test the null hypothesis of no treatment difference at six months. Confidence intervals and p-values can be extracted from this model directly. This model accounts for outcome data being missing under a missing at random assumption. We would not anticipate missing baseline data so will not use multiple imputation.

A pre-specified exploratory analysis will compare the clinical effectiveness of fludrocortisone with midodrine. This will use the same model as for the primary analysis.

8.2.2 Analysis of Secondary Outcome Measures

For secondary questionnaire and blood pressure outcomes we will use the same analysis as for the OHQ, except with the relevant baseline variable as a fixed effect instead of OHQ. For count variables (number of falls, number of fallers, number of syncopal events, number of hospitalisations) over 12 months we will use a negative binomial regression to allow for zero-inflation. This will be adjusted for age, aetiology and site. For time until first fall, a Cox regression model will be fitted adjusted for the same variables. Adverse Events will be tabulated by arm by type and severity.

8.2.3 Subgroup Analyses

For the primary outcome we will explore subgroup effects through including an interaction parameter in the primary analysis model described above. Variables we will consider are:

- Neurogenic OH and non-neurogenic OH
- Age ≥80 years versus age <80 years
- Male versus female
- Presence of diabetes versus no diabetes

8.2.4 Interim Analyses and Criteria for the Premature Termination of the Trial

An interim analysis will be conducted after 200 participants have been randomised. Prior to this, an interim statistical analysis plan will be developed that fully specifies the statistical methods to be used. Briefly, a linear mixed-effects model will be fitted to three-and six-month OHQ data, with fixed effects for baseline OHQ data, treatment assignment and random effects for individual. This model will be used to estimate the difference in six-month OHQ between fludrocortisone and control and between midodrine and control. If the estimated difference for an experimental arm is 0 or less (corresponding to the arm having worse outcome than control), it will be recommended to be dropped from the trial. This recommendation will be ratified by the TSC and the DMC.

If one experimental arm is recommended for dropping at the interim analysis and this is ratified by the DMC, the trial will continue to its planned enrolment, but subsequent participants will be randomised 1:1 between control and the remaining experimental arm.

If both experimental arms are recommended for dropping at the interim analysis and this is ratified by the DMC, the trial will be terminated early.

8.3 Sample Size Calculation

The trial is testing two null hypotheses: 1) the mean difference in six-month OHQ between fludrocortisone and control is ≤0; and 2) the mean difference in six-month OHQ between midodrine and control is ≤0.

With testing of each hypothesis at a two-sided 5% Type 1 error rate a three-arm trial without interim analyses would require n=309 participants with six month information, randomised 1:1:1 between the three arms, for 90% power. This assumes a standard deviation of 2.2 and minimally clinical informative difference (MCID) of 1.0 as found from the OHQ validation study [6] and confirmed by our PPI work.

The multi-arm design will control the total chance of falsely recommending an ineffective treatment (one-sided family-wise error rate, FWER) at 4.5%. With the possibility of early lack-of-benefit stopping, the FWER will be lower than this.
Assuming attrition of 15% (based on comparable clinical trials in older people of similar duration [33-37]) the recruitment target is 366 (122 per arm).
Taking into account the interim analysis, assuming that participants are recruited over a 30-month period with a staggered opening of sites, the power of the design to recommend each treatment is displayed in the table below (as determined from one million simulation replicates per scenario). This assumes only participants with six month data collected are included in the interim analysis. In practice including participants with three-month data but not yet six-month data will allow modest additional efficiency.

Scenario	Probability recommend fludrocortisone	Probability recommend midodrine	Probability recommend both	Probability recommend at least one
Mean effect of both = 0 (null scenario)	2.4%	2.4%	0.4%	4.4%
Fludrocortisone has MCID, midodrine effect = 0	91.8%	2.5%	2.5%	91.8%
Midodrine has MCID, fludrocortisone effect = 0	2.4%	91.7%	2.4%	91.7%
Both treatments have MCID effect	89.9%	89.7%	82.8%	96.8%

9. HEALTH ECONOMICS ANALYSIS

The study will include a within trial cost-utility analysis with longer-term model based extrapolation. For both the within trial analysis and the model based analysis the results will be reported as incremental costs, QALYs and incremental cost per QALY gained.

9.1 Within-trial Analysis of Costs and Outcomes

The within trial analysis cost and outcomes for the three trial intervention arms will be based on data collected over the 12-month follow-up period. Costs will be those that fall on the NHS, personal social services (PSS), participants and their families and will based upon use of health and social services and, as part of the costs falling on patients and their families, the time and travel costs of accessing services. Costs will also be collected at baseline for the use of primary care services for the three months prior to baseline solely to allow costs to be adjusted for any baseline imbalances in the use of services.

The use of secondary services will be collected via an eCRF. Use of primary health care and personal social services will be collected by self-administered Health and Social Service Use questionnaires at baseline, three, six, and twelve months. Costs to participants and their families for private health care

and time away from usual activities will also be collected via the questionnaire noted above. The cost of secondary care will be based on standard sources e.g. NHS reference costs, BNF. Standard sources will also be used to cost care provided in primary or social care. These unit costs will be combined with the use of services data to estimate costs for each participant.

The costs of accessing care by participants and their families will be based on responses to a time and travel questionnaire completed at six months. The focus of this questionnaire is on the time and monetary cost incurred the last time a specific type of health care was used (e.g. general practice visit or an outpatient visit). The responses to this questionnaire will be used to estimate the unit costs to the participant and their family of accessing each type of care. Travel costs will be based on costs reported by participants and also on data routine sources (e.g. mileage costs). The time costs will be valued according to the type of activity that accessing care is displacing (work or leisure time) and valued appropriately based on a review of the literature in the UK. These unit costs will then be combined with the use of services data to estimate costs of time and travel cost for each participant.

From the costs estimated at three, six, and twelve months for each participant estimates a mean cost to the NHS and PSS, participant and their families and overall in each arm of the trial for the 12-month follow-up period will be calculated.

Health status, measured using the EQ-5D-5L will be collected from participants at baseline, three, six and 12 months. A proxy version of EQ-5D-5L will be included to be used for participants who are unable to self-complete the questionnaire. With the proxy version, the caregiver is asked to rate how he/she thinks the patient would rate his/her own health-related quality of life, if the patient were able to communicate.

The response to the EQ-5D-5L will be converted into scores using population tariffs [38]. These will then be converted into QALYs for each participant using the area under the curve approach. From the QALYs estimated for each participant, the mean QALYs for each arm of the trial for the 12-month follow-up period will be estimated.

Using the data on total costs per participant regression techniques will be used to identify any difference between fludrocortisone or midodrine compared to usual care when controlling for (base line factors as outlined in the statistical analysis and for costs the cost of primary care in the three months prior to randomisation). A similar approach will be used to estimate the difference in QALYs between the treatment strategies.

The cost and QALY regressions will be run simultaneously using seemingly unrelated regression (SUR)[39]. SUR permits the simultaneous estimation of costs and effects, calculated at individual level, while accounting for unobserved individual characteristics that could affect both costs and QALYs and lead to potential correlation between these two dependent variables [40].

9.2 Model Based Analysis

An economic model will be used to extrapolate outcomes into the longer term. Outcomes of the model will be expressed in terms of costs to the NHS and PSS, QALYs and incremental cost per QALY gained. The model will be structured as when there is a choice about whether or not to start medical treatment and which medical treatment to start and follow individuals for the remainder of their life. The model will be developed in accordance with the NICE reference case [41]. We anticipate that the

model will take the form of a microsimulation as this will allow the best use of patient level data from the trial. The precise structure of the model will be developed during the project and will reflect the clinical decision question and the impact of OH. The trial data will be the main source of data but further data will be assembled from the literature and other existing data sources following guidance for best practice [42, 43]. Both costs and QALYs will be discounted in the base case at 3.5% [41]. Deterministic sensitivity analyses will include assessing the impact of different costs and utilities (e.g. cross walking EQ-5D-5L data to EQ-5D-3L scores), etc. Probabilistic sensitivity analysis will also be conducted. The results of this latter analysis will be presented as cost/QALY plots and cost effectiveness acceptability curves.

10. DATA HANDLING

10.1 Data Collection Tools and Source Document Identification

All data for an individual patient will be collected by each PI or their delegated nominees and recorded in the electronic case report form (eCRF) for the study. The study-specific eCRF will be set up using Sealed Envelope system. Patient identification on the eCRF will be through a unique study identifier number. A record linking the patient's name to the unique study identifier number will be held in a locked room at the study site, and is the responsibility of the PI. As such, patients cannot be identified from eCRFs. The NCTU Data Manager or nominated designee will continually monitor completeness and quality of data recording in eCRFs and will correspond regularly with site PIs (or their delegated assistants) with the aim of capturing any missing data where possible, and ensuring continuous high quality of data.

10.2 Data Handling and Record Keeping

Overall responsibility for data collection lies with the Chief Investigator. Data collected on paper Case Report Forms will be entered onto a secure validated clinical data management system. A unique study identifier will be used to identify participants on case report forms. Data will be handled, computerised and stored in accordance with the Data Protection Act 2018 and the General Data Protection Regulation. The quality and retention of study data will be the responsibility of the Chief Investigator. All study data will be retained in accordance with the latest Directive on GCP (2005/28/EC) and local policy.

The CDMS (Sealed Envelope) used for this trial is fully compliant with all regulatory frameworks for research of this nature. It uses a secure web-based interface for data entry; no data are stored on computers at site. The system has an inbuilt back-up facility, through Sealed Envelope's hosting partner Rackspace's secure premises in London, and is managed and supported by the Rackspace team.

Where there is electronic storage of non-identifiable data it will be on a password protected device and/or database.

The study questionnaires will be completed at each study visit by the patient, with the assistance of the research team if required, directly onto paper with subsequent transcription to the eCRF by site staff. If visits are being carried out remotely, questionnaires can be completed over the phone or videoconference by the clinician and participant, before being transcribed to the eCRF by site staff.

Questionnaires can also be posted to the participant, from the site, for completion by the participant and return to the site.

The falls diaries will be returned by the participants at study visits with falls data entered into the eCRF by site staff. If participants forget their falls diaries, they will be provided with a new diary to complete from that visit onwards and pre-paid addressed envelopes will be provided during the visit to post their completed diary back to site staff to facilitate timely data entry.

If study visits are conducted remotely, the information from the falls diary can be collected over the phone or video call and the falls diary posted back to the site team. A replacement falls diary can be provided to the participant via post.

Postural blood pressure will be assessed and reported at each study visit using one of the options in Section 5.4.1, documented in the medical notes and entered in to the eCRF.

The medical notes can act as source data for past medical history, medication use, subsequent medical conditions, hospital admissions, Adverse Events, blood pressure and blood results. The eCRF may act as the source data, for data entered to the Screening Log within the eCRF system.

10.3 Access to Data

Staff involved in the conduct of the study, including the PIs, trial management team and NHS staff involved in screening and intervention will have access to the Investigator Site Files (ISFs).

The study data and patient medical records may be looked at by monitoring or auditing personnel from an Independent Ethics Committee (IEC) or other regulatory authorities, the study Sponsor or the hospital Trust.

Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, the Data Monitoring Committee (DMC) or the REC. Secure anonymised electronic data will be released to the Study Statistician(s) for analysis. The PI and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

Role based access to the Sealed Envelope database will be granted to site PIs, their delegated site data entry personnel, and the NCTU trial management team for monitoring purposes.

10.4 Archiving

Data will be archived in accordance with the NCTU SOP and European Commission Directive 2005/28/EC Article 17. Essential data will be retained for a period of at least five years following close of trial in line with Sponsor policy and the latest Directive on GCP (2005/28/EC). Archiving will be authorised by the Sponsor following submission of the end of trial report. Authorisation will be requested from the Sponsor to destroy the documentation at the end of the archiving period.

11 MONITORING, AUDIT & INSPECTION

11.1 Trial Management

Trial Managers will oversee the study and will be accountable to NCTU and CI. The Data Manager will be responsible for checking the eCRFs for completeness, plausibility and consistency. However, this will remain the overall responsibility of the CI. Any queries will be resolved by the CI or delegated member of the trial team. The NCTU trial team will be supported by a Senior Trial Manager.

A study-specific Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

Each Research team member will be required to document study training on a study-specific training log which will be provided by NCTU.

11.2 Trial Management Group

The trial will be co-ordinated by a Trial Management Group, consisting of the grant holders, Sponsor, NCTU Management Team, Trial Statistician(s) and Health Economist(s). The group will meet monthly. Study site PIs and research nurses may be invited to attend selected TMG meetings.

11.3 Trial Steering Committee

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial; a lay representative will be included in the TSC. The terms of reference of the TSC and the draft template for reporting will be held in the TMF.

11.4 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of trial participants. The terms of reference of the DMC will be detailed in the TMF.

11.5 Inspection

The trial may be subject to audit by representatives of the Sponsor, Funder, MHRA or NIHR HTA. Each investigator site will permit trial-related monitoring, audits and regulatory inspection including access to all essential and source data relating to the trial.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Research Ethics Committee Review and Reports

The NCTU will obtain a favourable ethical opinion from a NHS REC prior to the start of the trial. All parties will conduct the trial in accordance with this ethical opinion.

NCTU will notify the REC of all required substantial amendments to the trial and those non-substantial amendments that result in a change to trial documentation. Substantial amendments that require a REC favourable opinion will not be implemented until this REC favourable opinion is obtained. The

NCTU will notify the REC of any serious breaches of GCP or the protocol, urgent safety measures or SUSARs that occur during the trial.

An annual progress report will be submitted each year to the REC by NCTU until the end of the trial. This report will be submitted within 30 days of the anniversary date on which the original favourable ethical opinion was granted.

The NCTU will notify the REC of the early termination or end of trial in accordance with the required timelines.

Before any site can enrol patients into the trial, that site must have received HRA approval as well as Confirmation of Capacity and Capability from the Site NHS Research and Development Department.

12.2 Peer Review

The trial has undergone Peer review through the process of grant application and funding award by the NIHR HTA Panel.

12.3 Public and Patient Involvement

As this is a commissioned study, the research question was pre-defined. Patient consultation influenced the choice of primary outcome, the timing of the primary outcome and the minimally important clinical difference required to judge treatment success. Study assessments have been tied into usual clinic appointment to reduce appointment burden.

Ongoing patient involvement will be coordinated by a Research Assistant who has experience working with these PPI members. At least one patient with OH will be appointed to the Trial Steering Committee. To increase involvement of frailer people with OH, the Research Assistant will visit patients in their own home to review documentation, meeting agendas and minutes and feed back to the TSC. This method of PPI engagement was chosen based on consultation with this patient group who expressed a wish to participate in PPI activities without leaving their home.

12.4 Regulatory Compliance

The trial will be conducted in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. All parties must abide by these regulations and the ICH GCP guidelines.

NCTU staff will obtain a Clinical Trial Authorisation (CTA) from the MHRA prior to the start of the trial and will notify the MHRA of any substantial amendments that require review by the competent authority. These substantial amendments will not be implemented until the MHRA has issued an acceptance of the amendment.

The Sponsor will notify the MHRA of any serious breaches of GCP or the protocol, urgent safety measures or SUSARs that occur during the trial.

The Development Safety Update Report will be submitted each year to the MHRA by NCTU staff, until the end of the trial.

NCTU staff will notify the MHRA of the early termination or end of trial in accordance with the required timelines.

12.5 Protocol Compliance

It is the responsibility of the CI to ensure that the clinical investigation is run in accordance with GCP and the protocol. Study tasks may be delegated to a suitably qualified or experienced member of the research team but the CI and PI will retain overall responsibility for adherence to protocol and GCP. The trial will be monitored by NCTU staff, to measure protocol compliance and manage deviations.

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials. The CI will not implement any deviation from the protocol without agreement from the Sponsor, except where necessary to eliminate an immediate hazard to trial participants.

In the event of a deviation from the protocol, the nature of and reasons for the deviation will be recorded on a deviation tracking log and signed off by the PI, NCTU will notify the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC, RA and local NHS R&D for review and approvals as appropriate. It is Sponsor policy that waivers to the protocol will not be approved.

For the purpose of avoiding uncertainty, the occurrence of a protocol deviation, breach or serious breach will not lead to withdrawal of the participant from the trial. Once randomised, participants will remain in the trial unless meeting the criteria for withdrawal given in Section 5.8.

12.6 Notification of Serious Breaches to GCP and/or the Protocol

Any violations must be reported to NCTU within three days of awareness. The Trial Manager will notify the Sponsor of all violations as soon as they become aware of them. Violations will be reviewed to determine if they meet the criteria for a serious breach. Where a serious breach has been identified, it is the responsibility of the Sponsor to notify the REC and MHRA within **seven calendar days** of determining that a serious breach has occurred.

A serious breach is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or
(b) the scientific value of the trial

12.7 Data Protection and Patient Confidentiality

All investigators and study site staff will comply with the General Data Protection Regulation, as it applies in the UK, with the Data Protection Act 2018, with regards to the collection, storage, processing and disclosure of personal information and will uphold the core principles of the legislation.

Study data held electronically will be accessible only by authorised study personnel and will be password protected. Paper records containing personal information will only be accessible by the

research team at each site, central study personnel, and auditors/inspectors from the Sponsor or regulatory authorities.

Data will be stored for five years following the end of the trial.

12.8 Indemnity

NHS indemnity for clinical trials conducted with NHS permission will apply for clinical negligence that harms individuals towards whom the NHS has a duty of care. Indemnity in respect of protocol authorship will be provided through a combination of NHS schemes (for those protocol authors who have substantive NHS employment contracts) and through Newcastle University's public liability insurance (for those who have their substantive contracts of employment with the University).

There is no provision for indemnity in respect of non-negligent harm. NHS Organisations must ensure that site staff without substantive NHS contracts hold honorary contracts to ensure they can access patients and are covered under the NHS indemnity arrangements.

12.9 Amendments

It is the responsibility of the Sponsor to determine whether an amendment is substantial or not and study procedures must not be changed without the mutual agreement of the CI, Sponsor and Trial Steering Committee.

Substantial amendments will be submitted to the REC and/or MHRA (as appropriate) and will not be implemented until this approval is in place. It is the responsibility of NCTU staff to submit substantial amendments after approval by the Sponsor.

Non-substantial amendments will be submitted to the Health Research Authority (HRA) and will not be implemented until authorisation is received.

Substantial amendments and those minor amendments which may impact sites will be submitted to the relevant NHS R&D Departments for notification to determine if the amendment affects the NHS permission for that site. Amendment documentation will be provided to sites by NCTU staff.

12.10 Post-Trial Care

All three treatment arms in this study are current clinical treatment strategies. If participants respond to their allocated treatment they will be able to continue with their treatment if judged appropriate by their usual clinician. Equally, participants may switch to an alternative treatment on exiting the study at the discretion of their clinician. No provision for continuation of study medications will be made by the trial team or Sponsor.

12.11 Access to the Final Trial Dataset

In accordance with The Newcastle Upon Tyne Hospitals NHS Foundation Trust, Government and NIHR policies, non-identifiable research data may be shared with researchers in other Universities and organisations (including those in other countries), for research in health and social care. If there is a need to share identifiable information, explicit consent will be sought from participants. Appropriate

safeguards will be in place where any identifiable information is transferred to other countries, in particular those countries with different data protection laws to the UK.

We are committed to sharing de-identified individual level data, where a rigorous research question may be answered by those data. The research team, including NCTU staff and the CI, will consider proposals from researchers as long as there is no constraint due to:

- Ethical approval and informed consent
- The NIHR contract
- The request does not require the data prior to publication of the main trial findings
- The request for data does not extend beyond that which is needed to answer the specific research question.

The CI is nominated by the Sponsor to take responsibility, as custodian of the data.

Ownership of the data arising from this study resides with Newcastle University. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared. A final study report will be available in the NIHR HTA Library.

The trial funder (NIHR) and Newcastle Clinical Trials Unit will be acknowledged within publications arising from this study and will have the right to review documents prior to publication.

The trial protocol will be published prior to completion of recruitment to the trial.

13 DISSEMINATION POLICY

13.1 End of Study Reporting

The end of study is defined as Last Patient Last Visit (LPLV) date.

The end of the study will be reported to the Sponsor, REC, HRA and NHS R&D Offices within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow-up is arranged for all participants.

A final report of the study will be provided to the Sponsor, REC and RA within one year of the end of the study.

The end of trial summary results will be uploaded to the European Clinical Trials Database (EudraCT) within 12 months of the end of study date.

Dissemination to the academic community will include a final report for the funders, as well as findings presented at international scientific meetings and submitted for publication in high-impact open-access peer-reviewed journals.

Dissemination to patients and our patient advisory group will include a number of the following methods: including publishing results on the study website, patient support groups' blogs and newsletters and regional public engagement events.

13.2 Authorship Policy

Authorship eligibility for each manuscript arising from this study will be determined by the Trial Management Group. All co-applicants, plus the Senior Trial Manager, Trial Managers, Data Manager, Trial Health Economist and Trial Statistician, will be eligible for authorship on papers reporting the protocol and main trial results, subject to fulfilling the ICMJE authorship criteria. Authorship for other conference abstracts and scientific papers arising from this work will be decided by the Trial Management Group.

13.3 Publication

The clinical study report will be used for publication and presentation at scientific meetings. Trial investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

13.4 Making Results Publicly Available

Trial results will be made publicly available on a trial registry within 12 months of the end of the trial, defined as Last Patient Last Visit date.

13.5 Data Sharing

At the end of the trial, a de-identified dataset will be prepared and stored by Newcastle University. Requests for data sharing with bona fide research teams outwith Newcastle University or NuTH will be considered and will be subject to presenting a clear plan of what the data will be used for, how the data will be analysed, 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.

14 REFERENCES

1. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, Cheshire WP, Chelimsky T, Cortelli P, Gibbons CH *et al*: **Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome**. *Clinical Autonomic Research* 2011, **21**(2):69-72.
2. Zhou Y, Ke SJ, Qiu XP, Liu LB: **Prevalence, risk factors, and prognosis of orthostatic hypotension in diabetic patients: A systematic review and meta-analysis**. *Medicine (Baltimore)* 2017, **96**(36):e8004.
3. Velseboer DC, de Haan RJ, Wieling W, Goldstein DS, de Bie RM: **Prevalence of orthostatic hypotension in Parkinson's disease: a systematic review and meta-analysis**. *Parkinsonism & Related Disorders* 2011, **17**(10):724-729.
4. Saedon NIz, Pin Tan M, Frith J: **The Prevalence of Orthostatic Hypotension: A Systematic Review and Meta-Analysis**. *The Journals of Gerontology: Series A* 2018:gly188-gly188.
5. Merola A, Sawyer RP, Artusi CA, Suri R, Berndt Z, Lopez-Castellanos JR, Vaughan J, Vizcarra JA, Romagnolo A, Espay AJ: **Orthostatic hypotension in Parkinson disease: Impact on health care utilization**. *Parkinsonism Relat Disord* 2018, **47**:45-49.

6. Kaufmann H, Malamut R, Norcliffe-Kaufmann L, Rosa K, Freeman R: **The Orthostatic Hypotension Questionnaire (OHQ): validation of a novel symptom assessment scale**. *Clin Auton Res* 2012, **22**(2):79-90.
7. Angelousi A, Girerd N, Benetos A, Frimat L, Gautier S, Weryha G, Boivin JM: **Association between orthostatic hypotension and cardiovascular risk, cerebrovascular risk, cognitive decline and falls as well as overall mortality: a systematic review and meta-analysis**. *J Hypertens* 2014, **32**(8):1562-1571.
8. Ricci F, Fedorowski A, Radico F, Romanello M, Tatasciore A, Di Nicola M, Zimarino M, De Caterina R: **Cardiovascular morbidity and mortality related to orthostatic hypotension: a meta-analysis of prospective observational studies**. *Eur Heart J* 2015, **36**(25):1609-1617.
9. McDonald C, Pearce M, Kerr SR, Newton J: **A prospective study of the association between orthostatic hypotension and falls: definition matters**. *Age Ageing* 2016.
10. Frith J, Elliott CS, Bashir A, Newton Jl: **Public and patient research priorities for orthostatic hypotension**. *Age and Ageing* 2014, **43**(6):865-868.
11. Frith J, Parry SW: **New Horizons in orthostatic hypotension**. *Age Ageing* 2017, **46**(2):168-174.
12. NICE [ESUOM20]: **Postural hypotension in adults: fludrocortisone**. *NICE Evidence summary* 2013.
13. NICE [ESNM61]: **Orthostatic hypotension due to autonomic dysfunction: midodrine**. *NICE Evidence summary* 2015.
14. **Prescribing Guideline for Management of Orthostatic (Postural) Hypotension** [https://www.hey.nhs.uk/wp/wp-content/uploads/2016/09/orthostaticPosturalHypotension.pdf]
15. **Midodrine prescribing guidelines** [file://campus/home/home38/njf26/Downloads/MidodrineGUI201510V1.0FINAL%23.pdf]
16. **SHARED CARE GUIDELINE FOR MIDODRINE IN POSTURAL HYPOTENSION** [https://doclibrary-rcht.cornwall.nhs.uk/DocumentsLibrary/RoyalCornwallHospitalsTrust/Clinical/Pharmacy/Midodrine.pdf]
17. Brignole M, Moya A, de Lange FJ, Deharo J-C, Elliott PM, Fanciulli A, Fedorowski A, Furlan R, Kenny RA, Martín A *et al*: **2018 ESC Guidelines for the diagnosis and management of syncope**. *European Heart Journal* 2018, **39**(21):1883-1948.
18. Logan IC, Witham MD: **Efficacy of treatments for orthostatic hypotension: a systematic review**. *Age and Ageing* 2012, **41**(5):587-594.
19. Mills PB, Fung CK, Travlos A, Krassioukov A: **Nonpharmacologic management of orthostatic hypotension: a systematic review**. *Arch Phys Med Rehabil* 2015, **96**(2):366-375 e366.
20. Ong AC, Myint PK, Shepstone L, Potter JF: **A systematic review of the pharmacological management of orthostatic hypotension**. *Int J Clin Pract* 2013, **67**(7):633-646.
21. Parsaik AK, Singh B, Altayar O, Mascarenhas SS, Singh SK, Erwin PJ, Murad MH: **Midodrine for orthostatic hypotension: a systematic review and meta-analysis of clinical trials**. *J Gen Intern Med* 2013, **28**(11):1496-1503.
22. Shibao C, Grijalva CG, Lipsitz LA, Biaggioni I, Griffin MR: **Early discontinuation of treatment in patients with orthostatic hypotension**. *Autonomic Neuroscience-Basic & Clinical* 2013, **177**(2):291-296.
23. Grijalva CG, Biaggioni I, Griffin MR, Shibao CA: **Fludrocortisone Is Associated With a Higher Risk of All-Cause Hospitalizations Compared With Midodrine in Patients With Orthostatic Hypotension**. *J Am Heart Assoc* 2017, **6**(10).
24. **Summary of product characteristics midodrine 2.5mg** [http://www.webcitation.org/70nuNIUUn]
25. Scottish Medicines Consortium: **Midodrine hydrochloride**. *https://wwwscottishmedicinesorguk/medicines-advice/midodrine-hydrochloride-bramox-abbreviatedsubmission-109415/* 2015, **Accessed 9 Nov 2018**.

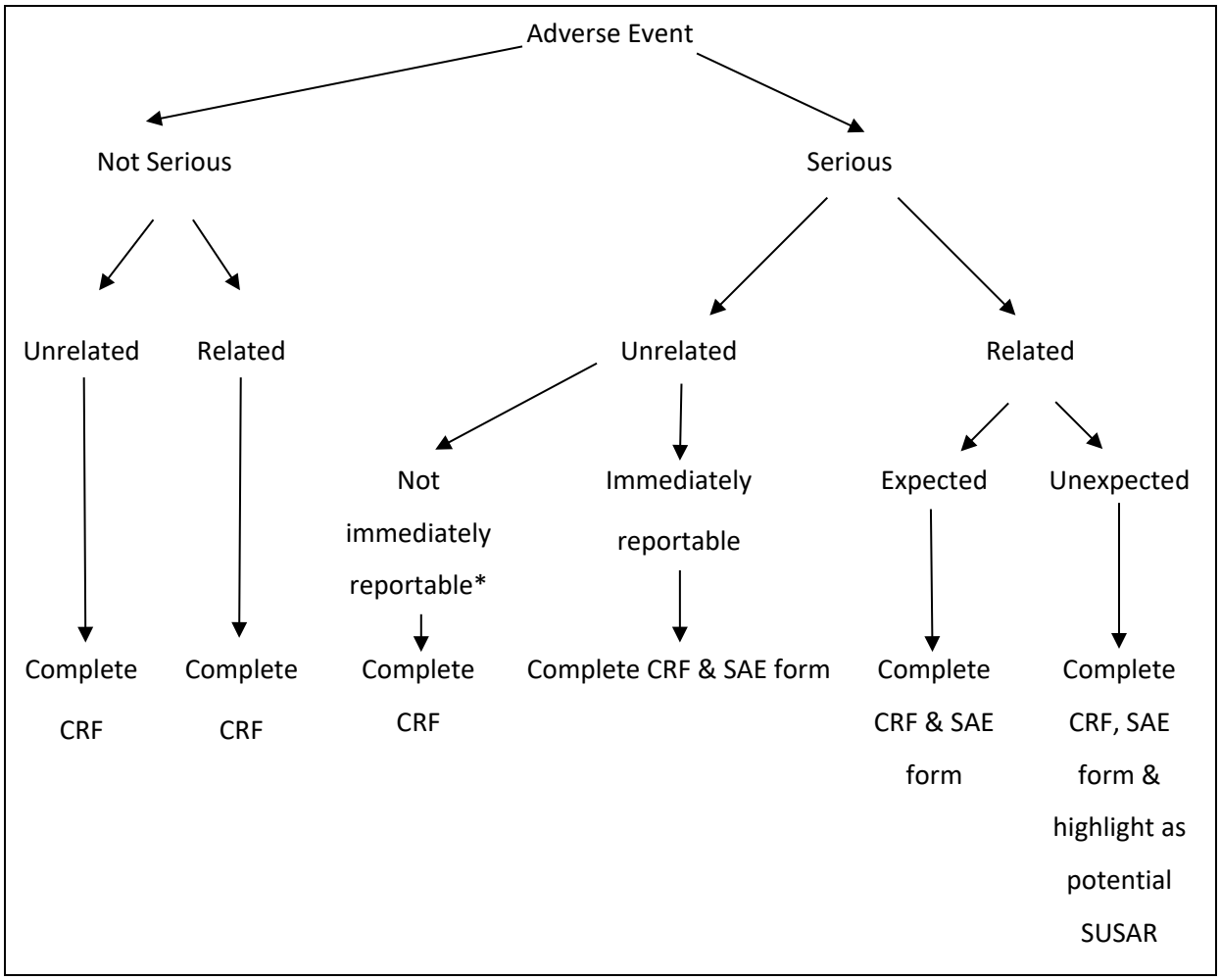
26. Frith J, Newton JL: **Validation of a questionnaire for orthostatic hypotension for routine clinical use**. *Geriatr Gerontol Int* 2016, **16**(7):785-790.
27. Thornicroft G: **An adapted version of the Client Service Receipt Inventory (CSRI; Beecham J & Knapp M)**, 2nd edn edn. London: Gaskell; 2001.
28. Ridyard CH, Hughes DA: **Methods for the collection of resource use data within clinical trials: a systematic review of studies funded by the UK Health Technology Assessment program**. *Value Health* 2010, **13**(8):867-872.
29. Thorn JC, Coast J, Cohen D, Hollingworth W, Knapp M, Noble SM, Ridyard C, Wordsworth S, Hughes D: **Resource-use measurement based on patient recall: issues and challenges for economic evaluation**. *Appl Health Econ Health Policy* 2013, **11**(3):155-161.
30. **EQ-5D-5L | Proxy version** [https://euroqol.org/eq-5d-instruments/eq-5d-5l-available-modes-of-administration/proxy/]
31. Gibbons CH, Schmidt P, Biaggioni I, Frazier-Mills C, Freeman R, Isaacson S, Karabin B, Kuritzky L, Lew M, Low P *et al*: **The recommendations of a consensus panel for the screening, diagnosis, and treatment of neurogenic orthostatic hypotension and associated supine hypertension**. *J Neurol* 2017, **264**(8):1567-1582.
32. Lahrmann H, Cortelli P, Hilz M, Mathias CJ, Struhal W, Tassinari M: **Orthostatic hypotension**. In: *European Handbook of Neurological Management.* Edited by Gilhus NE, vol. 1: Blackwell Publishing; 2011: 469-475.
33. Spice CL, Morotti W, George S, Dent THS, Rose J, Harris S, Gordon CJ: **The Winchester falls project: a randomised controlled trial of secondary prevention of falls in older people**. *Age & Ageing* 2009, **38**(1):33-40.
34. Ciaschini PM, Straus SE, Dolovich LR, Goeree RA, Leung KM, Woods CR, Zimmerman GM, Majumdar SR, Spadafora S, Fera LA *et al*: **Community-based intervention to optimise falls risk management: a randomised controlled trial**. *Age Ageing* 2009, **38**(6):724-730.
35. McMurdo ME, Roberts H, Parker S, Wyatt N, May H, Goodman C, Jackson S, Gladman J, O'Mahony S, Ali K *et al*: **Improving recruitment of older people to research through good practice**. *Age Ageing* 2011, **40**(6):659-665.
36. Witham MD, Price RJ, Struthers AD, Donnan PT, Messow CM, Ford I, McMurdo ME: **Cholecalciferol treatment to reduce blood pressure in older patients with isolated systolic hypertension: the VitDISH randomized controlled trial**. *JAMA Intern Med* 2013, **173**(18):1672-1679.
37. Sumukadas D, Price R, McMurdo MET, Rauchhaus P, Struthers A, McSwiggan S, Arnold G, Abboud R, Witham M: **The effect of perindopril on postural instability in older people with a history of falls—a randomised controlled trial**. *Age and Ageing* 2018, **47**(1):75-81.
38. **Valuing Health-Related Quality of Life: An EQ-5D-5L Value Set for England OHE Research Paper 16/01.** [https://www.ohe.org/publications/valuing-health-related-quality-life-eq-5d-5l-value-set-england#.]
39. Fiebig D: **Seemingly Unrelated Regression**. In: *A Companion to Theoretical Econometrics.* Maldon, MA, USA: Blackwell Publishing Ltd; 2007: 101-121.
40. Willan AR, Briggs AH, Hoch JS: **Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data**. *Health Econ* 2004, **13**(5):461-475.
41. **Guide to the methods of technology appraisal 2013** [https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-

2007975843781.]
42. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, Woolacoot N, Glanville J: **Review of guidelines for good practice in decision-analytic modelling in health technology assessment**. *Health Technol Assess* 2004, **8**(36):iii-iv, ix-xi, 1-158.

43. Caro JJ, Briggs AH, Siebert U, Kuntz KM: **Modeling good research practices--overview: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--1**. *Value Health* 2012, **15**(6):796-803.

15 APPENDICES

15.1 Appendix 1 - Safety Reporting Diagram



- Please refer to Section 7.7 for not immediately reportable SAEs

Contact details for reporting SAEs and SUSARs within 24 hours of becoming aware of the event

nctu.Conform-OH.sae@nhs.net (from a NHS.NET email account)

15.2 Appendix 2 – Amendment History

Amendment Number	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
N/A	1.0	04 Apr 2021	N/A	Initial Version however amended to V2.0 prior to approvals process and therefore never implemented at sites
N/A	2.0	02 Jun 2021	N/A	Initial version
SA01	3.0	30 Sep 2021	Gillian Watson	• Addition of ISRCTN to protocol (Protocol Research Reference Numbers Section); • Addition of trial website URL to protocol (Protocol Key Trial Contacts Section); • Addition of 'it is' (Protocol Section 1.2); • Clarification of recruitment of trial sites – change from 'open an additional two sites each month' to 'open an additional eight sites' (Protocol Section 3.2.1) • Clarification of the definition of 'pre-screening' and 'screening' for this trial, including addition of 'Eligibility' to Screening task in Schedule of Events (Protocol Sections 3.2.2, 3.4.2, 5.1, 5.5); • Clarification of randomisation system used: addition of 'integrated in Sealed Envelope', and 'via Sealed Envelope' (Protocol Sections 3.2.2, and 5.5); • First use of LSBP also given in full as Lying Standing Blood Pressure (Protocol Section 3.4.2); • Addition of 'and the' (Protocol Section 3.4.2); • Removal of exclusion criterion: 'Unable to stand upright without assistance', for clarification (Protocol Section 4.3); • Clarification of procedures for posting out questionnaires from site to participants, and return to site, once completed (Protocol Section 5.2); • Correction of 'These consist of…' to 'Baseline assessment consists of…' (Protocol Section 5.2);

				• Removal of 'with' (Protocol Section 5.3); • Relocation of paragraph 'At each consultation … data collection' within protocol section (Protocol Section 5.4.2) • Clarification of term 'Demographics', with further information: 'DoB, gender, ethnicity' (Protocol Section 5.5); • Clarification of the use of culprit medications (effectively the concomitant medications will take), versus IMP review. This includes the addition to the Schedule of Events in the protocol, of confirmation that the participant is taking IMP, at Baseline, six and 12 months (Protocol Sections 5.5, 6.1 and 6.8); • Clarification of data used at participant withdrawal, to include 'any future' routinely collected data and the assessment of any loss of capacity on a case-by-case basis (Protocol Section 5.7); • Addition of 'be' (Protocol Section 7.5); • Update to individual performing expectedness assessment of SARs, due to change in Sponsor process. This will be the CI, or in their absence a named delegate (Protocol Section 7.6, 7.9); Change of individual performing expectedness assessment of SARs (Sponsor requirement) • Addition of 'The eCRF may act as the source data, for data entered to the Screening Log within the eCRF system' (Protocol Section 10.2) • Correction, as deviations will not be recorded in the eCRF; removal of 'These deviations will also be captured in the eCRF' (Protocol Section 12.5); • Addition of 'H' to make HRA (Protocol Section 13.1) • Removal of BP Monitor instructions, as they do not relate to the model of BP Monitor to be used in the trial. Stand-alone instructions will be provided separately. (Protocol Appendix 3);
	4.0	04 Jan 2022	Gillian Watson	• Update to Table of Contents • Addition of Appendix 2 – Amendment History
	5.0	24 Feb 2022	Gillian Watson	• Changes to trial personnel • Update of name of NHS Trust • Addition of re-screening if deemed necessary by Physician

				• Addition of further drugs to be checked for at each visit • Change of timescale for patient consideration of trial participation • Clarification of sample size calculation section • Change to way the 20 trial sites will be opened • Clarification of what constitutes trial procedures, and what is acceptable on Consent Forms • Clarification of procedure for use of eligibility and baseline BP measurements