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**Trial Title:** Optimising Prescription of Treatment In older patients with Mild hypertension at Increased risk of Serious adverse Events

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There are no conflicts of interest relating to this trial from the Chief Investigator and/or delegates

#### **Confidentiality Statement**

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee and Regulatory/Competent Authority/ies unless authorised to do so.

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## 2. LAY SUMMARY

### *Background*

More than one in three adults aged 75+ years are prescribed five or more drugs to treat their long-term conditions. People who take lots of drugs are more likely to end up with reduced independence and quality of life as they get older. They are also more likely to end up in hospital due to drug side effects. One solution is to stop or 'deprescribe' drugs which no longer provide benefit, or could be potentially harmful.

The most commonly prescribed drugs in older people are those used to lower blood pressure. These drugs reduce the risk of a stroke and heart attack. However, in some frail older people, they might also be harmful, causing kidney problems and fainting (leading to serious falls). This could cancel out any potential benefits of treatment. This uncertainty makes blood pressure lowering drugs an ideal target for deprescribing. However, very little research has been done in this area.

We have completed the largest trial of blood pressure drug deprescribing to date, and whilst successful, the study only included 569 participants and 12 weeks of follow-up. Currently, we do not know if deprescribing is safe or effective in the longer term (a year or more).

### *Aims*

This trial will establish whether deprescribing common drugs that lower blood pressure is safe in older people. We will answer:

1. What is the effect of deprescribing blood pressure lowering drugs on hospital admissions and death?
2. Does deprescribing affect health-related quality of life?
3. Does deprescribing offer value for money for the NHS?

### *Methods*

We will carry out a trial aiming to enrol 3,014 participants and actively follow them up for one year. Volunteer participants will be aged 75 years or older and taking blood pressure lowering drugs, but not have raised blood pressure readings. We will focus on those who are frail and/or with a higher risk of serious drug related side-effects. The trial will examine whether deprescribing is safe in this group, by measuring how many people are admitted to hospital or die in the year after having blood pressure lowering drugs withdrawn. This number will be compared to the number of people who are admitted or die among those who have not had their medications withdrawn. If the numbers are similar, then deprescribing will be viewed as safe. If considered safe at 12 months, a decision will be made with the Trial committees and funders to continue the trial and passively follow-up participants using their electronic health records for up to 10 years (subject to further funding) to see whether deprescribing reduces hospital admissions over that longer time period. We will also check if deprescribing affects quality of life and/or costs for the NHS.

### *Dissemination*

Results from this work will be communicated to key audiences through scientific journals, patient summaries and presentations at scientific meetings and community engagement events. Some time after the trial has finished the results will be published on the trial website. Participants will be contacted to notify them that the results have been published and giving them the weblink to the results.

### 3. SYNOPSIS

<b>Trial Title</b>	Optimising Prescription of Treatment In older patients with Mild hypertension at Increased risk of Serious adverse Events		
<b>Short title</b>	OPTIMISE2		
<b>Trial registration</b>	ISRCTN18030225		
<b>Sponsor</b>	University of Oxford Research Governance, Ethics & Assurance Team (RGEA) University of Oxford, Boundary Brook House, Churchill Drive, Headington, Oxford OX3 7GB		
<b>Funder</b>	National Institute for Health Research (NIHR) Health Technology Assessment		
<b>Clinical Phase</b>	Phase IV trial		
<b>Trial Design</b>	Primary Care based, open label, randomised controlled trial		
<b>Trial Participants</b>	Patients aged $\geq 75$ years, with controlled systolic blood pressure ( $<140$ or $<150$ mmHg depending on age) receiving $\geq 2$ antihypertensive medications and at higher risk of hypotension, syncope, falls and/or fracture ( $\geq 5\%$ risk in the next 5 years) and/or with moderate to severe frailty (eFI score of $\geq 0.20$ ).		
<b>Planned Sample Size</b>	3,014 (plus any patients who are waiting for a consent visit once 3,014 participants have been randomised)		
<b>Planned Trial Period</b>	01/04/2023 – 30/04/2027		
<b>Planned Recruitment period</b>	01/04/2023 – 30/06/2026		
	<b>Objectives</b>	<b>Outcome Measures</b>	<b>Timepoint</b>
<b>Primary outcome</b>	To determine if antihypertensive deprescribing results in a percentage of patients with an emergency hospitalisation or dying which is non-inferior (within 5%) to that observed under usual care	Emergency hospitalisation or death	1 year
<b>Intervention</b>	Step down medication reduction, maintaining a systolic blood pressure below a target of 150 mmHg (or $<140$ mmHg in those aged 75-79 years). Choice of medications to be withdrawn will be at the discretion of the consulting GP (or qualified and appropriately trained health professional responsible for hypertension care or medicines management), based on indications, co-morbidities, blood pressure and guidance from the trial team.		
<b>Comparator</b>	Usual care (no medication changes mandated).		

#### 4. ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ACEI	Angiotensin-Converting Enzyme Inhibitors
ADR	Adverse drug reaction
AE	Adverse event
AR	Adverse reaction
ADWE	Adverse drug withdrawal event
CI	Chief Investigator
CPRD	Clinical Practice Research Datalink
CRF	Case Report Form
CRN	Clinical Research Network
CSR	Clinical Study Report
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CVD	Cardiovascular Disease
DMEC	Data Monitoring and Ethics Committee
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
eFI	Electronic Frailty Index
EMIS	Egton Medical Information Systems
GCP	Good Clinical Practice
GP	General Practitioner
HES	Hospital Episode Statistics
HRA	Health Research Authority
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational Medicinal Product
IRB	Independent Review Board
LVSD	Left Ventricular Systolic Dysfunction
MHRA	Medicines and Healthcare products Regulatory Agency
mmHg	millimetres of mercury
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
OPERAM	Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults
OPTiMISE	OPtimising Treatment for MIld Systolic hypertension in the Elderly
OPTIMISE2	Optimising Prescription of Treatment In older patients with Mild hypertension at Increased risk of Serious adverse Events
ORCHID	Oxford Royal College of General Practitioners Clinical Informatics Digital Hub
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
QALY	Quality-Adjusted Life Year
QOF	Quality and Outcomes Framework
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RES	Research Ethics Service
RGEA	Research Governance, Ethics and Assurance
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
STRATIFY	STRAtifying Treatments In the multi-morbid Frail elderly
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TSC	Trial Steering Committee

## 5. BACKGROUND AND RATIONALE

### *What is the problem being addressed?*

More than one in three adults aged 75+ years are prescribed  $\geq 5$  medications,<sup>1</sup> a situation known as polypharmacy. This is associated with multi-morbidity, reduced independence and decreased health-related quality of life in older people.<sup>2-4</sup> *Inappropriate* polypharmacy (too many medications given the number and type of conditions present)<sup>5</sup> is associated with an increased risk of hospital admission due to adverse drug reactions (ADRs), which account for approximately 10% of all admissions.<sup>6,7</sup>

One approach to managing polypharmacy and reducing ADRs is to withdraw (deprescribe) medications where the risk of adverse events is high and the likelihood of benefit is small (i.e. the benefit to harm ratio is unfavourable).<sup>8</sup> However, trials of deprescribing have so far failed to demonstrate reductions in death, hospitalisation or improvements in health-related quality of life, primarily due to small sample sizes and limited follow-up.<sup>9,10</sup> Most have examined complex interventions, such as pharmacist-led medication reviews, where the type of drugs removed vary widely, making translation into clinical practice difficult.<sup>10,11</sup> In many of these trials, actual deprescribing was limited; for example, in the recently published OPERAM trial of hospital based drug optimisation in older adults with multi-morbidity, only 52% of deprescribing recommendations were implemented by treating healthcare professionals.<sup>11</sup> Thus, a more focused approach may be required, targeting specific drug classes.

Antihypertensives are the most frequently prescribed medication in patients with polypharmacy.<sup>1</sup> Individual patient data meta-analyses of randomised controlled trials have shown that antihypertensives reduce the risk of cardiovascular disease (CVD), with the largest benefits seen in older people.<sup>12</sup> However, inclusion and exclusion criteria used in these studies mean that they may not be representative of those with frailty and multi-morbidity.<sup>13</sup> Clinical guidelines<sup>14-17</sup> therefore recommend caution when prescribing antihypertensives in older adults, due to the potential risk of adverse events, but until recently, the extent to which antihypertensives cause harm was unknown. We therefore conducted a systematic review to examine this, searching Embase, MEDLINE, CENTRAL, and the Science Citation Index from inception until 14<sup>th</sup> April 2020, for randomised controlled trials reporting the association between antihypertensive treatment and serious adverse events including falls and acute kidney injury.<sup>18</sup> Across 58 eligible trials, including 280,638 participants, blood pressure lowering therapy was associated with an increased number of adverse events, including acute kidney injury, hypotension and syncope, but not falls.<sup>18</sup>

Many of the trials examined in our review focussed on younger age groups (mean age of included participants ranged from 37-84 years), and it was not possible to examine how these effects changed by age, frailty or morbidity status, due to the risk of ecological bias.<sup>19</sup> We undertook further observational analyses using data from 3.8 million patients within the Clinical Practice Research Datalink (CPRD) to explore these associations in more detail.<sup>20</sup> Patients with a qualifying systolic blood pressure between 130-179 mmHg were included and followed-up for up to 10 years. In time to event analyses, using propensity scores to adjust for confounding, antihypertensives were associated with an increased risk of hospitalisation or death from falls (HR 1.23, 95% Confidence Interval 1.21-1.26), hypotension (HR 1.32, 95% CI 1.29-1.35), syncope (HR 1.20, 95% CI 1.17-1.22), AKI (HR 1.44, 95% CI 1.41-1.47), electrolyte abnormalities (HR 1.42, 95% CI 1.43-1.48) and gout (HR 1.35, 95% CI 1.32-1.37).<sup>20</sup> The absolute risk of SAEs with treatment was very low, with six fall events per 10,000 patients treated per year. In older patients (80-89 years) and those with severe frailty, this risk was increased, with 61 and 84 fall events per 10,000 patients treated per year (respectively).<sup>20</sup> This increasing risk of harm, combined with the fact that blood pressure can be closely monitored following drug withdrawal, makes antihypertensives the ideal drug class to focus on in this trial.

*What is the current evidence for deprescribing antihypertensives in older people?*

A recent Cochrane review found just six trials of antihypertensive deprescribing in patients aged 50 years or older (including 1,073 participants) with a maximum follow-up of 56 weeks.<sup>21</sup> The trials included in this review reported very few outcome events of interest, and therefore was underpowered to show any association between antihypertensive deprescribing and mortality (18 events), cardiovascular mortality (3

events), hospitalisation (19 events) or falls (0 events). More recently, our OPTiMISE trial<sup>22</sup> showed that antihypertensive deprescribing could be achieved without affecting NICE recommended systolic blood pressure control (<150 mmHg for age  $\geq 80$ ) at 12-weeks follow-up. No differences were observed in serious adverse events or health-related quality of life, although blood pressure did increase modestly (3/2 mmHg) in the deprescribing group compared to control.<sup>22</sup> The trial was limited to 12 weeks of follow-up for ethical reasons, to demonstrate the short-term effects of medication reduction on blood pressure and adverse events prior to embarking on a larger trial as now proposed with longer follow-up.

We subsequently undertook a follow-up systematic review, searching the literature for any more recent studies examining the effects of antihypertensive deprescribing, focussing on older patients aged 75 years or above. We searched MEDLINE, Embase, and CENTRAL databases from inception to 24<sup>th</sup> May 2021, identifying just three eligible trials. Only two of these reported all cause hospitalisation (just 47 events) and the association with deprescribing remained inconclusive. Similarly, there were too few events to determine the association between antihypertensive deprescribing and mortality (8 events) or cardiovascular disease outcomes (2-10 events), emphasising the urgent need for an appropriately powered trial.

There are currently two ongoing trials examining the longer-term effects of antihypertensive deprescribing.<sup>23,24</sup> The RETREAT-FRAIL trial,<sup>24</sup> being conducted in France, aims to recruit 1,100 patients with low blood pressure (<130 mmHg) at the end of life, residing in nursing homes and is powered to detect differences in mortality. Similarly, the OptimizeBP study<sup>23</sup> is being undertaken in 383 older patients residing in long-term care facilities in the Alberta region of Canada. This trial is also powered to detect a difference in mortality following pharmacist initiated antihypertensive medication reduction. These trials will not determine the effects of targeted deprescribing in community dwelling older people with multimorbidity, where larger potential benefits of deprescribing could be realised from intervening earlier. Furthermore, our PPI consultations suggest that mortality is not the most important endpoint in this group. The present proposal will focus on a broader population (see below), and examine patient morbidity through a combined outcome comprising mortality or emergency hospital admission, establishing whether antihypertensive deprescribing is safe and cost-effective.

Some deprescribing interventions, including pharmacist-led approaches for reducing non-steroidal anti-inflammatory drugs, have been shown to be cost-effective in community dwelling older adults.<sup>25</sup> However, since the efficacy of antihypertensive deprescribing is poorly understood, there are no studies examining whether it is a cost-effective strategy. For deprescribing to be adopted as an evidence-based approach in routine clinical practice, a strong evidence base including the economic case for why it should be attempted is needed. This needs robust, long-term follow-up data to take into account the potential target population, the benefits and harms of deprescribing, evidence surrounding its economic effects and evidence on how such an intervention would be implemented in routine clinical practice.

#### *Evidence explaining why this research is needed now*

In England, approximately 1.5 million adults aged 75+ years are prescribed  $\geq 5$  medications,<sup>1,26</sup> and around 250,000 non-elective NHS hospital admissions (costing £530 million) are thought to be related to potentially avoidable ADRs, every year.<sup>27</sup> A key priority is therefore to optimise medicines use in older people and reduce the burden of ADRs, aligned with the NHS long term plan to support healthy ageing.<sup>28</sup> Deprescribing antihypertensives could address this need by reducing polypharmacy, but only if the balance of risks (potential increase in CVD events) and benefits (potential reduction in ADRs) is improved.

Deprescribing is increasingly being promoted in clinical guidelines<sup>14,15,27</sup> and clinical care,<sup>29,30</sup> but this may be premature. This is emphasised by the recent Cochrane review of antihypertensive deprescribing cited previously,<sup>21</sup> which concluded that deprescribing may be safe, but that there are very few data on clinical endpoints. There is therefore a need for an appropriately powered, high quality randomised controlled trial examining the benefits, safety and cost-effectiveness of this approach using pragmatic generalisable methods in primary care.<sup>15</sup>

*Rationale for focusing on patients at high risk of adverse events*

Several trials and meta-analyses have shown that antihypertensives reduce cardiovascular events in older people who have been randomized in treatment trials.<sup>12,31,32</sup> However, such trials include only a minority of participants similar to the wider population of community dwelling people currently receiving antihypertensive treatment.<sup>13</sup> In particular, those who are more likely to suffer adverse drug events, including those who are frail, were not generally included in treatment trials and may not benefit from ongoing antihypertensive treatment.

In order to understand these issues more, we undertook a decision modelling based economic evaluation as part of our previous OPTiMISE trial.<sup>22,33</sup> This showed that deprescribing antihypertensive medication in **all** adults aged 80 years or older is unlikely to be a cost-effective intervention due, in part, to the increased risk of cardiovascular events resulting from the small increase in blood pressure observed in the original trial. In this analysis, usual care was associated with increased economic costs in comparison to deprescribing, but was considered the more cost-effective of the two strategies. However, in sensitivity analyses, deprescribing became cost-effective (lower overall economic costs with a similar quality-adjusted life year (QALY) profile, on average) if targeted at individuals with a higher risk of serious adverse events. Although these analyses were based on estimates and extrapolations with significant uncertainty, they suggest a targeted approach to antihypertensive deprescribing may be the most cost-effective strategy.

## 6. OBJECTIVES AND OUTCOME MEASURES

This trial will examine whether there is a non-inferior difference in emergency hospital admission and all-cause death at 1 year from deprescribing antihypertensives in older adults at risk of an adverse event. If this is shown, then the trial will continue and assess whether there are differences in time to emergency hospital admission or death at 3 years after randomisation and then at 5 and 10 years post-randomisation (subject to further funding). A linked cost-effectiveness analysis will assess the short and long-term impacts of deprescribing antihypertensives. ICD-10/11 coded definitions for each outcome of interest can be found in Appendix A.

Objectives	Outcome Measures	Timepoint(s)
<b>Primary</b> To determine if antihypertensive deprescribing results in a percentage of patients with an emergency hospitalisation or death during follow-up which is non-inferior (within 5%) to	Emergency hospitalisation (all-cause admissions which are unpredictable and at short notice because of clinical need; 'method of admission' codes 21-25 and 28 [admission for at least 1 day overnight]) or death	1 year post-randomisation

	that observed under usual care		
<b>Secondary (Clinical events)</b>	Determine the difference in major cardiovascular events resulting in hospitalisation or death between randomised groups at 1 year follow-up	Proportion of participants experiencing major cardiovascular events resulting in hospitalisation (Four-point definition: non-fatal acute myocardial infarction, non-fatal stroke, non-fatal heart failure and cardiovascular death) during follow-up (see appendix A for codes)	1 year post-randomisation
	Determine the difference in the percentage of participants experiencing a cardiovascular death between randomised groups	Cardiovascular death (primary cause of death; see appendix A for codes)	1 year post-randomisation
	Determine the difference in the percentage of participants experiencing all-cause death between randomised groups	All-cause death	1 year post-randomisation
	Determine the difference in the percentage of participants experiencing all-cause emergency hospitalisation between randomised groups	All-cause emergency hospitalisation	1 year post-randomisation
	Determine the difference in the percentage of participants experiencing all-cause hospitalisation between randomised groups	All-cause hospitalisation	1 year post-randomisation
	Determine the difference in the percentage of participants experiencing a myocardial infarction resulting in hospitalisation or death between randomised groups	Acute myocardial infarction resulting in hospitalisation or death (see appendix A for codes)	1 year post-randomisation
	Determine the difference in the percentage of participants experiencing a stroke resulting in hospitalisation or death between randomised groups	Stroke resulting in hospitalisation or death (see appendix A for codes)	1 year post-randomisation
	Determine the difference in the percentage of participants experiencing heart failure resulting in hospitalisation or	Heart failure resulting in hospitalisation or death (see appendix A for codes)	1 year post-randomisation

	death between randomised groups		
	Determine the difference in the percentage of participants experiencing serious falls resulting in hospitalisation or death between randomised groups	Fall resulting in hospitalisation or death (see appendix A for codes)	1 year post-randomisation
	Determine the difference in the percentage of participants experiencing serious hypotension resulting in hospitalisation or death between randomised groups	Hypotension resulting in hospitalisation or death (see appendix A for codes)	1 year post-randomisation
	Determine the difference in the percentage of participants experiencing serious syncope resulting in hospitalisation or death between randomised groups	Syncope resulting in hospitalisation or death (see appendix A for codes)	1 year post-randomisation
	Determine the difference in the percentage of participants experiencing serious fracture resulting in hospitalisation or death between randomised groups	Fracture resulting in hospitalisation or death (see appendix A for codes)	1 year post-randomisation
	Determine the difference in the percentage of participants experiencing dementia resulting in hospitalisation or death between randomised groups	Dementia resulting in hospitalisation or death (see appendix A for codes)	1 year post-randomisation
	Determine the difference in the percentage of participants experiencing a serious adverse event between the randomised groups	Serious Adverse Event	1 year post-randomisation
	Determine the difference in the percentage of participants experiencing a non-serious adverse event of interest between randomised groups	Non-serious adverse events of interest* (not resulting in hospitalisation or death)  *outlined in Appendix F	1 year post-randomisation
	Determine the difference in the percentage of participants experiencing an adverse drug	Adverse drug withdrawal event	4 weeks post-randomisation

	withdrawal event (ADWE) between randomised groups		
	Determine the difference in the percentage of participants admitted to a nursing home or long term care facility between randomised groups	Admission to a nursing home or long term care facility	1 year post-randomisation
<b>Secondary (Medication)</b>	Determine the difference in average treatment burden between randomised groups	Multimorbidity treatment burden score	1 year post-randomisation
	Determine the difference in average medication burden between randomised groups	Number of medications prescribed (medication burden)	1 year post-randomisation
	Determine the difference in average antihypertensive medication between randomised groups	Number of antihypertensive medications prescribed	1 year post-randomisation
	Determine the percentage of patients in intervention arm who maintain medication reduction through to follow-up ( <i>i.e.</i> are <i>not</i> restarted on therapy)	Proportion of patients randomised to the intervention arm who maintain medication reduction throughout 1 year follow-up.	1 year post-randomisation
<b>Secondary (Physiological measures)</b>	Determine the difference in average blood pressure between randomised groups	Systolic and diastolic blood pressure	1 year post-randomisation
	Determine the difference in the percentage of participants experiencing symptoms between randomised groups	Symptoms (based on the Revised illness perception questionnaire) <sup>34</sup>	1 year post-randomisation
<b>Secondary (Patient reported outcomes)</b>	Determine the difference in health-related quality of life outcomes between randomised groups	EQ-5D-5L index <sup>35</sup> and visual analogue scale	1 year post-randomisation
	Determine the difference in the percentage of participants with a physical disability between randomised groups	Loss of at least one ADL <sup>36, 58</sup>	1 year post-randomisation
<b>Secondary (Long term follow-up)</b>	Determine the difference in the percentage of participants experiencing clinical events (described above) between the randomised groups at 3, 5 and 10 year follow-up	Clinical events described above	3, 5 and 10 years post-randomisation (subject to further funding)

<b>Tertiary</b>	Examine the impact of participant attitudes towards deprescribing at baseline on adherence to protocol	Protocol Adherence	1 year post-randomisation
	Determine the cost-effectiveness of implementing deprescribing over the trial follow-up period	Costs associated with patient identification, monitoring activities and any follow-up/management, change in quality adjusted life years (QALYs) as determined by follow-up questionnaires	Trial follow-up period encompassing one year post-randomisation
	Determine the long-term cost-effectiveness of deprescribing	Proportion estimated to experience cardiovascular disease event; falls; incremental cost per QALY gained; probability of cost-effectiveness; net monetary benefit.	Lifetime time horizon encompassing data collected within trial and extrapolation of trial outcomes
<b>Exploratory Objectives</b>	Subgroup analysis determining the difference in the percentage of participants experiencing emergency hospitalisation or dying in the intervention and usual care groups by baseline age (75-79 vs 80+ years), ethnicity (white vs non-white), and frailty status (mild/moderate vs severe frailty)	Emergency hospitalisation or death	1 year post-randomisation
	Subgroup analyses determining the difference in the percentage of participants experiencing emergency hospitalisation or death by STRATIFY-Hypotension/Syncope/ Falls risk	Emergency hospitalisation or death	1 year post-randomisation

## 7. TRIAL DESIGN

This trial will use a primary care based, individually randomised, controlled, non-inferiority design, based on the trial design successfully tested and implemented in our previous OPTiMISE study.<sup>22</sup> An embedded health economic evaluation will include a within-trial economic evaluation, as well as a decision-analytic modelling economic evaluation that adapts the Markov model developed in the original OPTiMISE study.<sup>37</sup>

This trial will be undertaken in a primary care setting, within approximately 200 general practices across all regions of the NIHR Research Delivery Network in England. The primary care setting will enable all

potentially eligible participants to be identified and approached, and permit examination of the intervention, in the setting in which it will be delivered in routine clinical practice. To enable efficient capture of trial outcomes, participants will be recruited either from practices using electronic health record systems (e.g. EMIS or SystmOne) or those contributing to the Oxford Royal College of General Practitioners Clinical Informatics Digital Hub (ORCHID).<sup>38</sup> ORCHID is a database of primary care electronic health records (linked to hospital episode statistics [HES] and civil registration death data) and includes 1,858 contributing practices with over 15 million patients at the time of writing (<https://orchid.phc.ox.ac.uk>). This system permits near real-time collection of coded primary care data, prescriptions, and hospital admissions.<sup>39</sup> We will create automated searches to extract relevant data for participants and run these within each participating practice. These will be developed in collaboration with PRIMIS, a primary care informatics specialist based at the University of Nottingham.

Participants will be expected to attend a baseline recruitment and randomisation visit, and subsequent 4 weekly safety follow-up visits (1 per antihypertensive deprescribed; appendix B and C). Subsequent follow-up data will be collected via routine electronic health records and patients will not be expected to attend any further research follow-up appointments. Questionnaires (format depending on patient preference) will be sent to participants at 1 year post randomisation.

## 8. PARTICIPANT IDENTIFICATION

### 8.1. Trial Participants

The population of interest is adults aged  $\geq 75$  years with controlled systolic blood pressure ( $<140$  mmHg if aged 75-79 years or  $<150$  mmHg if aged  $\geq 80$  years), receiving two or more antihypertensive medications and at higher risk of serious adverse events.

### 8.2. Inclusion Criteria

- Willing and able to give informed consent for participation in the trial (or with Personal Legal Representative consent)
- Willing and able to report any safety concerns or with a suitable carer able to report these if unable
- Registered at either a practice using electronic health record systems (e.g. EMIS or SystmOne) or contributing to or willing to contribute to ORCHID<sup>38</sup>
- Aged 75 years or above at recruitment.
- Controlled systolic blood pressure, defined (in accordance with NICE 2019 guidelines)<sup>16</sup> as less than 140 mmHg (if aged 75-79 years) or less than 150 mmHg (if aged 80 years or above). Systolic blood pressure level will be based on screening measurements taken at baseline (mean of the 2<sup>nd</sup> and 3<sup>rd</sup> readings taken in a standardised manner) or from patient records.<sup>40</sup>
- Prescribed two or more antihypertensive medications for at least 12 months prior to trial entry. Antihypertensive medications defined as any ACE inhibitor, angiotensin II receptor blocker, calcium channel blocker, thiazide and thiazide-like diuretic (including loop diuretics), potassium-sparing diuretic, alpha-blocker, beta-blocker, vasodilator antihypertensives, centrally acting antihypertensives, direct renin inhibitors, adrenergic neurone blocking drugs.
- Stable dose of antihypertensive medications for at least four weeks prior to trial entry.

- Moderate or severe frailty (defined by an eFI score  $\geq 0.20$ )<sup>41</sup> and/or high risk (>5%) of hypotension, syncope or falls in the next 5 years, based on STRATIFY risk prediction algorithms<sup>42,43</sup> applied to an individual's electronic health record.

### 8.3. Exclusion Criteria

- Heart failure due to left ventricular systolic dysfunction (LVSD) prescribed only ACE inhibitors/angiotensin II receptor blockers and/or beta-blockers and/or spironolactone (removing any of which would be contraindicated).
- Heart failure diagnosis without a coded echocardiogram (might have undiagnosed LVSD and a compelling need for ACEI/ angiotensin II receptor blocker and beta-blockers).
- Suffered a myocardial infarction or stroke within the past 6 months.
- Secondary hypertension or previous accelerated or malignant hypertension.
- Lacking capacity to give consent and without a Personal Legal Representative present at the point of screening.
- Investigator deems that there is a compelling indication for medication continuation.
- Participating in any other randomised controlled trial of drug treatment or interventional medical devices in the past 4 weeks (can be re-invited subsequently).

## 9. TRIAL PROCEDURES

A schedule of procedures can be found in Appendix B and C.

### 9.1. Recruitment

#### 9.1.1. Practice Recruitment

The trial will recruit from all regions of the NIHR Research Delivery Network (RDN) in England aiming to achieve a geographically representative population. Furthermore, areas with more deprivation and diverse populations will be specifically targeted following discussion with the RDN. All practices will be approached by the trial team and/or the NIHR RDN detailing the trial and the GP/practice staff involvement is required.

#### 9.1.2. Practice database searches

Searches will be designed using trial inclusion/exclusion criteria and implemented within individual practices using query tools embedded within electronic health record systems (e.g. EMIS Recruit, PRIMIS automated searches). This will include application of the STRATIFY-Hypotension/Syncope/Falls clinical prediction algorithms<sup>42,43</sup> (see appendix D for predictors included in these algorithms), and the electronic frailty index<sup>41</sup>. These query tools will also be used to collect follow-up data where appropriate. Reports from these searches will be used by GPs (or qualified and appropriately trained health professional responsible for hypertension care or medicines management) to undertake a manual eligibility check prior to finalising the list of potentially eligible participants and sending of invitation letters. These reports may first be checked by another member of the GP Practice or network research teams provided that the GP (or qualified and appropriately trained health professional responsible for hypertension care or medicines management) reviews and finalises the list prior to sending the invitations. Pseudonymised data extracted for this part of the trial will also be used to describe the overall population and the proportion of those registered who are eligible to participate in the trial.

Where available, potentially eligible patients will be identified by application of the trial inclusion/exclusion criteria to the most recent data extract of the ORCHID database (appendix B and E). Patients meeting the criteria for trial eligibility through ORCHID will be flagged and their Care Record IDs will be passed onto participating GPs (or qualified and appropriately trained health professional responsible for hypertension care or medicines management) for manual checking of eligibility. These Care Record IDs are unique within each practice but not across the ORCHID database as a whole, meaning that individuals can only be identified by their consulting GP (or qualified and appropriately trained health professional responsible for hypertension care or medicines management), with access to their original medical records, but not by the research team who will not have this access prior to individual participant consent.

### **9.1.3. Patient Recruitment**

Those deemed eligible will be sent invitations from their GP using CFH DocMail. CFH DocMail is an online mail management solution for letter printing and mailing using secure servers. DocMail has been approved by the University of Oxford for use in trials and has extensive security accreditation. GPs may also choose to send a text message to potentially eligible patients directing them to the trial website to read the full invitation letter. Patients interested in participating will be asked to return an expression of interest slip by post (in prepaid envelopes marked as confidential and organised according to the University of Oxford's postal guidelines) or to contact the trial team directly via phone or secure email giving permission to be contacted to book a baseline visit. They will be asked some pre-screening questions by the trial team (e.g. confirmation of age, the number of blood pressure lowering medications they are taking, etc.) and then invited to attend a screening, recruitment and baseline clinic at their general practice (see flow chart in Appendix B). Where in-person visits are not possible (e.g. due to a pandemic related lockdown or for individuals with limited mobility who are unable to travel to face-to-face appointments), some or all of this screening, recruitment and baseline clinic will be undertaken via telephone/video call, with clinical data being extracted directly from the participant's electronic health record. Video calls made by GPs will be using their own pre-approved software which will have gone through IG processes for clinical use.

If response rates for a site are low, patients not responding to the first invitation may receive one reminder (up to four weeks after the initial invite) or if possible, a direct telephone call inviting them to participate. Where possible, telephone follow-up will be undertaken by multi-lingual nurses in areas where the local population includes a high proportion of ethnic minority groups. Telephone interpretation services may be used if required, if so, these will be approved for use by the University of Oxford and appropriate data retention arrangements put in place. All follow-up telephone calls will be made by practice staff and potential participants will not be contacted directly by research staff until they have expressed an interest in participating in the trial. Potentially eligible patients may also be approached opportunistically by a member of the clinical care team at a routine clinical follow-up appointment, or during a (nursing) home visit.

Each person booked for a baseline visit will receive a written participant information leaflet (PIL) describing why they have been invited, what they will be asked to do, what the intervention involves, what the risks and benefits of participation are, and what they should do if there are any problems or they would like to withdraw from the trial. The information leaflets will be written in a minimum of Arial 14 font and

formatted using an easy-to-follow structure developed with input from older patients as part of the original OPTIMISE study.<sup>22</sup> This will include summary pages at the beginning which sign post to more detailed information later on in the document. All individuals attending a screening visit will have been sent a copy of the patient information leaflet, the carers' information leaflet and example copy of the consent form, so that they have a chance to look at it prior to attending the clinic. In the case of last-minute appointments, or where the patient did not receive the documents before their appointment, the site team will ensure they are given adequate time to read these prior to the consent discussion. A short video infographic will also be created describing key elements of the trial for GPs (or qualified and appropriately trained health professional responsible for hypertension care or medicines management) to show to participants at the baseline appointment. If some or all of the baseline visit is remote, participants will be sent a link to view the video online.

## 9.2. Informed Consent

Informed consent will be received by the GP (or qualified and appropriately trained health professional responsible for hypertension care or medicines management), after which baseline screening measurements and data collection will be undertaken by a practice/research nurse or other appropriately trained and qualified researcher. Prior to the appointment, participating GPs (or qualified and appropriately trained health professional responsible for hypertension care or medicines management) will review the participant's current antihypertensive medication regime and decide which medication(s) should be removed if the participant is randomised to the intervention arm of the trial (see details of the intervention below). The choice of medication(s) to be reduced, and reasons why, will be documented and passed on to the practice/research nurse/researcher. The participant will not be informed of the choice of medication unless they are randomised to the intervention group. During the visit, GPs (or qualified and appropriately trained health professional responsible for hypertension care or medicines management) will show the video infographic and go through the full participant information leaflet explaining the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol and any risks involved in taking part.

Having discussed the trial with the GPs (or qualified and appropriately trained health professional responsible for hypertension care or medicines management), and having had a chance to ask questions, those individuals willing to participate will be asked to give informed consent. The patient will have read the participant information leaflet which details the trial, what is required of participants, discusses potential risks and benefits and provides contact details of the research team. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

Given the older age of the population being studied, GPs (or qualified and appropriately trained health professional responsible for hypertension care or medicines management) will be allocated up to 20 minutes to explain the trial to potential participants (standard trials would usually allocate 10 minutes), plus an additional 10 mins prior to meeting with the participant, to assess suitability and decide on the appropriate medication for withdrawal (30 mins per patient in total). The participant will be allowed as much time as they wish to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. Individuals with dementia and those lacking capacity to give informed consent (as determined by their GP) will not be excluded and consent from a Personal Legal Representative will be sought. A Personal Legal

Representative is defined under the Clinical Trials Regulations and is an individual not connected with the conduct of the trial who is suitable to act as the legal representative by virtue of their relationship with the adult, and is available and willing to do so. This person may provide consent to trial inclusion if the patient lacks capacity to consent to participate. The Personal Legal Representative will need to attend the baseline visit with the participant so that they have access to the same explanatory information and are able to discuss the trial with the GP and ask any questions they may have. Patients lacking capacity to give informed consent and without a Personal Legal Representative present at the point of screening and consent will not be eligible, but they will be invited to attend another baseline appointment if this can be booked with a Personal Legal Representative in attendance.

Written Informed Consent will be obtained by means of participant (or Personal Legal Representative) dated signature and dated signature of the person who presented and received the Informed Consent. There will be one consent form designed to include a section for participant signature or another for Personal Legal Representative signature, explaining that a Personal Legal Representative is signing on their behalf and believes that the participant would consent were they able. The GP (or qualified and appropriately trained health professional responsible for hypertension care or medicines management) who received the consent must be suitably qualified (*i.e.* have received training in GCP) and experienced, and have been authorised to do so on the delegation log by the Principal Investigator. The participant or Personal Legal Representative must personally sign and date the latest approved version of the Informed Consent form on 3-part no carbon required (NCR) paper before any trial specific procedures are performed. A copy of the signed Informed Consent will be given to the participant or Personal Legal Representative. The original signed form will be sent to the PC CTU, one copy retained at site and one with the participant/Personal Legal Representative.

Where some or all of an in-person baseline visit is not possible (e.g. due to a pandemic related lockdown or for individuals with limited mobility who are unable to travel to face-to-face appointments), consent may also be received remotely using the remote online electronic consent form available as part of the REDCap eCRF system and by telephone/video discussion. Where consent is received remotely, as part of a virtual consultation, eConsent will be used with participants/Personal Legal Representatives sent a customised email directly from the eCRF system containing a link to the eConsent page. They will be asked to provide a handwritten signature using a finger or a stylus or biometric eSignature on their tablet, mobile phone or other electronic device. Participants and/or their Personal Legal Representatives without access to a secure email account will be unable to consent remotely and would need to attend a face-to-face baseline visit.

Participants/Personal Legal Representatives will be given a copy of their consent form after completion, the original will be sent to the central trial team, and a copy kept at site/filed in patients' medical notes. For consent that is received digitally within REDCap (handwritten signature using a finger or a stylus or biometric eSignatures), a copy of the consent form will be emailed to the participant/Personal Legal Representative using an email address provided by them. The eConsent form will be downloaded from REDCap by the site research team and retained in the Investigator Site File/medical notes and a copy downloaded and held securely by the central trial team.

### 9.3. Screening and Eligibility Assessment

Those giving informed consent will then complete the screening procedures with a trained member of the research team/practice staff. These will include confirmation of the patient's age, past medical history (e.g.

history of stroke or heart attack in the past 6 months), current prescribed medication, and measurement of blood pressure. Patients not meeting certain eligibility criteria ( blood pressure out of range, not on a stable dose of antihypertensive treatment, recent myocardial infarction or stroke, no legal representative in attendance, or participating in another trial) will be invited back for re-screening within 4 weeks or once the required time has passed for eligibility. There is no limit on the number of re-screening visits permitted, so long as the participant is happy to return each time. Where in-person visits are not possible, this screening assessment will be undertaken via telephone/video call, with clinical data (including the last recorded blood pressure reading) being extracted directly from the participant's electronic health record or participants measuring their own blood pressure at home if possible.

Protocol waivers will not be permitted.

#### **9.4. Baseline Assessments**

Baseline data will be collected following confirmation of eligibility via patient questionnaires and a detailed notes review conducted by the research team/practice staff. Variables to be collected are listed below in Appendix C. During in-person visits, blood pressure will be measured using a clinically validated blood pressure monitor. Readings will be taken after participants have been seated for five minutes of rest and the mean of the 2<sup>nd</sup> and 3<sup>rd</sup> readings will be used to define trial eligibility. To test for orthostatic hypotension, two further readings will be taken in the standing position, immediately, and after three minutes.<sup>44</sup> Where baseline visits are undertaken remotely, participants will be encouraged to measure their own blood pressure if they have their own monitor and are comfortable taking readings. Otherwise, the last recorded clinic blood pressure will be used to determine eligibility during remote baseline visits.

Patient characteristics and information about their medical history will be extracted from the practice records by the research team/practice staff and entered directly into the trial database. Patients will be asked to complete questionnaires measuring quality of life, medication burden, cognitive and physical function (see details of measures in appendix C). Questionnaires will be available in electronic and paper format and participants will be given the opportunity to complete the form with which they are most comfortable. If completed online the questionnaires will be directly entered into the eCRF via a personal weblink emailed directly to the participant. If the questionnaires are completed on paper the participants will be provided with a prepaid, confidential envelope in which to return them once completed. The trial team will be available via telephone to help the participants complete the questionnaires if required, in which case they may directly enter the answers into the eCRF. If a Personal Legal Representative has consented on behalf of the participant then this representative may also complete the questionnaires with them or on their behalf where appropriate.

#### **9.5. Randomisation**

Participants will not be randomised until after consent and baseline eligibility assessments have been completed. Stratified randomisation will be used to individually allocate participants (1:1) to one of the two trial groups using a fully validated web-based randomisation system (Sortition) with stratification factors age (i.e. 75-79 and ≥80 years) and region of England. Randomly permuted block sizes will be used within strata.

#### **9.6. Blinding and code-breaking**

The trial will use an open label design, so patients and practitioners will not be blinded to the intervention or endpoints but analysis of outcomes will be blinded to the intervention allocation. Thus, codebreaking will not be necessary.

## 9.7. Subsequent Visits

All participants, regardless of group allocation, will be invited back to see a member of the clinical care team for a four-week safety follow-up visit to check blood pressure levels and capture any reportable safety events as outlined in Section 12. Those randomised to medication reduction may have further medications deprescribed at this point. If this occurs, another safety follow-up visit would be required after four weeks (safety visits continue at 4-weekly intervals per medication reduced). No subsequent research follow-up clinics will be conducted. Participants will receive questionnaires at 12 months post randomisation and all other data will be captured via electronic health records.

- 1. Safety visit (4 weeks after randomisation):** All participants (regardless of randomised group) will be asked to return to their GP practice to have their blood pressure checked, complete the Illness Perception Questionnaire Symptom List, and to report any adverse events that may have occurred. These visits should be scheduled as close to 4 weeks as possible while allowing for clinic room and participant availability. To ensure the safety of participants, blood pressure readings must be taken in person. This visit cannot be done remotely, however, these visits can be conducted as home visits if site capacity allows for patients who are housebound. If the participant is prevented from attending a 4 week safety visit due to mobility issues following an SAE (e.g. a fracture which renders them temporarily housebound) and a home visit is not possible then existing (home or hospital) BP readings should be used if they are available in the electronic health records until an in-person safety visit can be scheduled.

For those in the intervention arm whose blood pressure remains well controlled up to a target blood pressure of <150 mmHg (or <140mmHg for those 75-79), the person performing the visit should refer to the medication reduction plan and deprescribe a further antihypertensive if indicated. GPs (or qualified and appropriately trained health professional responsible for hypertension care or medicines management) are encouraged to consider deprescribing multiple antihypertensives, one at a time, where deemed appropriate and to outline this fully on the medication reduction plan, along with any monitoring considerations. If another medication is deprescribed, participants will be asked to attend a further safety visit 4 weeks later. Blood pressures collected during this visit will be entered into the participant's electronic health record and collected for the trial at follow-up. Adverse events of interest and those outlined in Section 12 reported during this (or any other visit) will be captured on a trial specific reporting form and sent directly to the research team for monitoring.

- 2. (a) Health outcomes follow-up (12 months after randomisation):** All health outcome follow-up data will be collected via direct reporting of AEs/SAEs, the ORCHID database or practice specific database searches and linked hospital episode statistics and civil registration death data from NHS England. These data will only include those required to meet study endpoints. NHS numbers collected at baseline will be used to flag participants in the ORCHID database using a hashing algorithm which protects an individual's personal data and maintains the anonymity of the ORCHID database. These NHS numbers and one other identifier will also be given to NHS England

along with a unique Trial ID for the trial cohort. NHS England will send back to University of Oxford the pseudonymised linked cohort data with HES and mortality data included. The University of Nottingham's PRIMIS team will also extract data from GP Practice systems for transfer to the trial team at University of Oxford. PRIMIS will have an agreement in place with the University of Oxford and each practice for this data extraction and will not review or store the data. This will be detailed on the consent forms. The University of Oxford will store these data in a secure location and process these data to determine outcomes of the trial.

2. **(b) Questionnaire follow-up (12 months after randomisation):** Participants will be given the option to receive questionnaires in the format most convenient to them either online or sent via secure post. If completing the questionnaires electronically participants will be sent an email directly from the RedCap eCRF system with a link to the questionnaire. If participants would prefer to receive this by post then a paper copy will be sent via secure post with an included prepaid return envelope marked confidential for them to return once completed. We will use telephone or meeting systems such as MS Teams to keep in touch with participants and assist them in completing these questionnaires. Any systems used by the central trial team will have been approved for use by the University of Oxford. Site staff would use internal GP systems which will have gone through their own information governance processes. Audio recordings will not be used for this trial. For those not comfortable using computers or apps, the research team will call participants to support them in completing these questionnaires by going through each question with them, reading it aloud and giving time to answer (with breaks where required). Follow-up questionnaires will be used to determine changes in outcomes (detailed in section 6; see appendix C).
3. **Longer-term follow-up (12-120 months after randomisation dependent on funding):** After 1 year of active follow-up to determine primary and secondary outcomes, all participants will continue to receive usual care which includes yearly blood pressure checks to ensure maintenance of blood pressure control and medication reviews. Provided the primary outcome is non-inferior to usual care at the end of active follow-up in the trial (e.g. 12 months post randomisation), a decision will be made (in conjunction with the Trial Steering Committee [TSC], Data Monitoring and Ethics Committee [DMEC] and funders) to continue to follow-up participants 'passively' via practice specific database searches or via ORCHID, with assessment of study outcomes at 3 years, 5 years and 10 years post randomisation (dependent on funding).

## 9.8. Sample Handling

No samples will be collected during the trial.

## 9.9. Internal Pilot Study

During the initial pilot phase, a total of 500 participants will be enrolled over six months, with 25 in the first month rising to approximately 120 participants per month by month six. This rate is expected to continue to increase to 130 participants per month by month 10, and then continue until the end of the recruitment period (27 months). This will require an increase in numbers of local CRNs, starting with 3 and building to cover all by month 10.

**Table.** Progression criteria from internal pilot to full trial.

Progression criteria	Not viable	Red	Amber	Green
Total number of participants recruited	<250	250-374	375-499	≥500
Trial recruitment % complete	<50%	50-74%	75-99%	100%
Recruitment rate/ site/ month	<1	1	1.5	≥2
Number of sites opened	<20	20-34	35-49	≥50

Proposed length of internal pilot phase: 6 months from first recruit

The feasibility of the trial will be assessed with an interim datalock six months after the first participant has been randomised according to criteria listed in the table above. During analysis of the pilot study, recruitment will continue unless advised to stop by the Trial Steering Committee (TSC). If all **Green** criteria are met, the trial will proceed as planned. If one or more **Amber** criteria are met, the recruitment approach will be re-examined with discussions with stakeholders and PPI representatives. If one or more **Red** criteria are met, the number of sites and eligibility criteria will be re-examined. If all red criteria are met, a decision will be made as to whether the trial remains feasible, in discussion with the Data Monitoring and Ethics Committee (DMEC), TSC and funder. Less than 50% recruitment will be considered not viable.

#### 9.10. Early Discontinuation/Withdrawal of Participants

During the course of the trial a participant may choose to withdraw early at any time. This may happen for a number of reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable adverse event
- Inability to comply with trial procedures
- Participant decision

Participants may choose to stop intervention measures and/or trial assessments but may remain on trial follow-up. Participants may also withdraw their consent, meaning that they wish to withdraw from the trial completely. In this situation, participants will have the following options for withdrawal;

- 1) Participants may withdraw from active follow-up (with questionnaires) and further communication but allow the trial team to continue to access their medical records and any relevant data that is recorded as part of routine standard of care.
- 2) Participants can withdraw from the trial but permit data obtained up until the point of withdrawal to be retained for use in the analysis. No further data would be collected after withdrawal.

In addition, the Investigator may discontinue a participant from the trial treatment at any time if they consider it necessary for any reason including, but not limited to:

- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- Significant protocol deviation
- An adverse event which results in inability to continue to comply with trial procedures

The proportion of patients who successfully maintain medication reduction is a secondary outcome of this trial and thus capturing this accurately at follow-up is important. Unless a participant withdraws consent for further data collection beyond the point of withdrawal, data required for trial endpoints will be

assessed even where an individual has been lost to follow-up (for instance moved away). The reason for withdrawal will be recorded in the CRF. If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

### **9.11. Definition of End of Trial**

The end of trial is the point at which all the data (collected actively and passively) has been entered into the study database and queries have been resolved.

## **10. TRIAL INTERVENTIONS**

This trial will examine the safety, efficacy and cost-effectiveness of antihypertensive deprescribing. This will consist of a step-down medication reduction approach, permitting multiple antihypertensives to be removed up to a target of <150 mmHg (or <140 in those aged under 80 years). Those allocated to the control group will receive usual clinical care, with no medication changes mandated. No other medication changes will be mandated and participating GPs (or qualified and appropriately trained health professional responsible for hypertension care or medicines management) will be asked to manage all other care according to usual clinical practice.

### **10.1. Investigational Medicinal Product(s) (IMP) Description**

Participants allocated to the intervention group of the trial will have at least one whole antihypertensive medication stopped with the potential for others to be removed sequentially at four week intervals, provided the participant and GP (or qualified and appropriately trained health professional responsible for hypertension care or medicines management) remain content to continue and the participant's systolic blood pressure remains below guideline recommended levels (<140 mm Hg in those aged 75-79 years; <150 in those aged 80+ years). The order of drugs to be stopped will be at the discretion of the consulting GP (or qualified and appropriately trained health professional responsible for hypertension care or medicines management), in line with existing guidelines. Participating GPs (or qualified and appropriately trained health professional responsible for hypertension care or medicines management) will be given a medication reduction algorithm (Appendix G) advising on which drugs to stop first, in line with approaches taken in previous studies.<sup>45,46</sup> The decision to reduce antihypertensive medication will require medical input based on indications, co-morbidities and blood pressure and whilst the trial team will provide the aforementioned withdrawal algorithm, the final decision will be left to the consulting GPs (or qualified and appropriately trained health professional responsible for hypertension care or medicines management).

To maintain fidelity of the intervention, each medication should be completely stopped, regardless of type or dose. Gradual dose reduction is not warranted, since any effects of withdrawing medication will be captured at the four-week safety visit. The only exception to this is when withdrawing beta-blockers or clonidine, where the dose should be reduced first to avoid rebound adrenergic hypersensitivity.

Once a medication has been removed, GPs (or qualified and appropriately trained health professional responsible for hypertension care or medicines management) will be expected to closely monitor the participant's response to medication reduction carefully. They will be given advice about what and when to monitor (Appendix H) but flexibility will be allowed to ensure the participant is managed in the way deemed most appropriate by their GP (or qualified and appropriately trained health professional

responsible for hypertension care or medicines management). Any additional monitoring requirements should be documented on the medication reduction plan for reference. Broadly speaking, all participants (regardless of randomised group) will be expected to return to their GP practice for at least one routine safety follow-up visit around 4 weeks after randomisation. If systolic blood pressure (3 readings, mean of 2<sup>nd</sup>/3<sup>rd</sup> reading) increases beyond what is considered clinically safe ( $\geq 140$  mm Hg in those aged 75-79 years;  $\geq 150$  in those aged 80+ years)<sup>47</sup> during this visit, the participant will be asked to return for further safety follow-ups and if the raised blood pressure persists, or adverse events occur, GPs/other appropriate, delegated healthcare professionals will be expected to re-adjust medication (dose or type) in line with Appendix H, rendering the likelihood of a serious adverse event occurring very low.

In the event that participating in this trial affects a practice's ability to meet QOF targets (*i.e.* those which recommend treatment to targets in specific patient subgroups which may not be met if antihypertensive medication is reduced), it will be recommended that relevant patients are exception reported as "not suitable" in all related QOF submissions.

#### **10.1.1. Blinding of IMPs**

There will be no blinding of IMPs in this trial.

#### **10.1.2. Compliance with Trial Treatment**

Since this is a trial of medication reduction, compliance with the trial treatment will involve not taking the medication which has been de-prescribed. Because individuals in the intervention arm will not be given a prescription for the de-prescribed medication, it will be hard for them not to comply and take therapy they should not be taking, unless they have a supply of tablets from prior to the de-prescribing of treatment. Participants randomised to medication reduction will be informed which medication the GP has recommended deprescribing and be asked to return them to their local pharmacy. There are no validated instruments for measuring compliance with medication reduction. GP prescribing data will be collected from electronic health records as a measure of compliance with the trial protocol.

#### **10.1.3. Accountability of the Trial Treatment**

Not applicable for this trial. No IMP or placebo is being prescribed to account for, only reduction of medications previously prescribed and accounted for as part of usual NHS care.

#### **10.1.4. Concomitant Medication**

Management of all other (non-blood pressure lowering) medication taken by participants will be at the discretion of participating GPs (or qualified and appropriately trained health professional responsible for hypertension care or medicines management). No other medication changes will be mandated and participating GPs will be asked to manage all other care according to usual clinical practice. Over the counter aspirin and statin medication taken will be recorded at baseline and follow-up.

#### **10.1.5. Post-trial Treatment**

Continuation (or not) of the intervention (medication reduction) after 1 year of active follow-up is complete will be at the discretion of the consulting GPs (or qualified and appropriately trained health professional responsible for hypertension care or medicines management). The participant remains the responsibility of their GP (or qualified and appropriately trained health professional responsible for hypertension care or medicines management) during and after the trial, and therefore post trial treatment will continue under normal care. At final follow-up, participating patients will be sign posted back to their clinical teams.

### **10.2. Control group**

Those allocated to the control arm of the trial will continue usual clinical care (i.e. they will continue to take antihypertensive medications as prescribed). No other medication changes will be mandated and participating GPs (or qualified and appropriately trained health professional responsible for hypertension care or medicines management) will be asked to manage all other care according usual clinical practice.

### **10.3. Other Treatments (non-IMPs)**

No non-IMPs will be provided during the trial.

### **10.4. Other Interventions**

No additional interventions will be provided during the trial.

## **11. ECONOMIC EVALUATION**

In order to provide decision-makers with the best available evidence on whether or not to adopt deprescribing of antihypertensives into routine clinical practice, it is important that evidence around its cost-effectiveness is established. An economic evaluation will be conducted in this study aiming to identify, measure and value the costs and consequences of deprescribing, and synthesise the evidence using metrics amenable to cost-effectiveness based decision-making. Two forms of economic evaluation will be conducted: (i) a within-trial economic evaluation of deprescribing that mirrors the time horizon of the non-inferiority trial; and (ii) a decision-analytic modelling-based economic evaluation that will extend over a lifetime horizon. The economic assessment methods will adhere to the recommendations of the National Institute for Health and Care Excellence (NICE) Reference Case.<sup>48</sup> A health economic analysis plan with full details of the planned economic evaluation will be drafted early in the trial and finalised and signed off by the Trial Steering Committee prior to any primary outcome analysis.

**Within-trial economic evaluation:** A within-trial economic evaluation, conducted from the recommended NHS and personal social services perspective,<sup>48</sup> will be embedded within the OPTIMISE2 trial design. Primary research will be undertaken to estimate the cost of implementing deprescribing, including the costs associated with patient identification, monitoring activities and any follow-up/management. Broader resource utilisation will be captured through two principal sources: (i) the electronic primary care health records and linked Hospital Episode Statistics; and (ii) Client Service Receipt Inventory questionnaires completed as described above at follow-up. Unit costs for resource inputs will largely be derived from national reference tariffs. Responses to participant EQ-5D-5L questionnaires completed at baseline and 12 months post-randomisation will be converted into health utilities using established utility algorithms<sup>49</sup> for the purposes of quality-adjusted life year (QALY) estimation with QALY profiles estimated using the trapezoid rule.

Bivariate regression of costs and QALYs, with multiple imputation of missing data, will be conducted to generate within-trial estimates of incremental cost-effectiveness associated with deprescribing. Sensitivity analyses will be undertaken to assess the impact of areas of uncertainty surrounding components of the economic evaluation. The sensitivity analyses will include re-estimation of cost-effectiveness based on cases with complete data, and re-estimation of cost-effectiveness assuming a broader societal perspective. The latter will incorporate direct costs to trial participants, economic values for informal care provided by

family and friends and economic values associated with productivity losses. Cost-effectiveness acceptability curves will be used to show the probability of cost-effectiveness of deprescribing at alternative cost-effectiveness thresholds held by decision-makers. Heterogeneity in the trial population will be explored by formulating net-benefit values for trial participants from the observed costs and effects and then constructing a regression model with an intervention variable and covariates such as age and sex (i.e. gender assigned at birth). The magnitude and significance of the coefficients on the interactions between the covariates and the intervention variable will provide estimates of cost-effectiveness of the deprescribing strategy by participant subgroup.

**Decision modelling-based economic evaluation:** Decision-analytic modelling will be used to extrapolate the impact of deprescribing of antihypertensives beyond the follow-up period of the main quantitative evaluation. Accepted guidelines for good practice in decision-analytic modelling will be followed.<sup>50</sup> The evaluation will adopt an NHS and personal social services perspective and costs and consequences accrued beyond the first year of follow-up will be discounted at a rate of 3.5% per annum. We will adapt our Markov model developed for the original OPTiMISE study<sup>37</sup> to estimate the effects of changes in prescribing on clinical endpoints such as serious adverse events and major cardiovascular events. By attaching NHS and personal social service costs (£, current prices at the point of analysis) and age and sex-specific health utility values (expressed in terms of mapped EQ-5D-3L health utilities) to each model health state, we will estimate the impact of deprescribing on lifetime costs and QALYs with cost-effectiveness expressed in terms of incremental cost per QALY gained. Multi-parameter uncertainty in the model will be addressed using probabilistic sensitivity analysis.<sup>51</sup> The values of parameter inputs into the model will draw upon the best available information from the literature to supplement the trial data.

Cost-effectiveness acceptability curves will be used to show the probability of cost-effectiveness of deprescribing at alternative cost-effectiveness thresholds held by decision-makers (typically £20,000 per QALY).<sup>52</sup> Sensitivity analyses will examine the minimal level of adverse event risk required at baseline for deprescribing to be accepted as a cost-effective strategy.

## 12. SAFETY REPORTING

The safety reporting window for the trial will be defined as the period between randomisation and 12 month follow-up for each participant in the trial. The AE reporting procedures are detailed below and summarised in appendix F. Investigators will be expected to follow up AEs deemed to be related to the trial intervention until event resolution or stabilisation. All other AEs should be followed-up until the end of the trial safety reporting window (12 months after randomisation). If a participant withdraws from the trial but still has adverse events ongoing then permission will be asked to continue this follow-up while withdrawing them from other aspects of the trial.

### 12.1. Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant
Adverse Reaction (AR)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered (or taken away), including occurrences which are not necessarily caused by or related to that product.

	<p>The phrase "response to an investigational medicinal product" means that a causal relationship between a trial intervention (discontinuation of antihypertensive medication) and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.</p> <p>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.</p>
Serious Adverse Event (SAE)	<p>A serious adverse event is any untoward medical occurrence that:</p> <ul style="list-style-type: none"> <li>• results in death</li> <li>• is life-threatening</li> <li>• requires inpatient hospitalisation or prolongation of existing hospitalisation</li> <li>• results in persistent or significant disability/incapacity</li> <li>• consists of a congenital anomaly or birth defect.</li> </ul> <p>Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.</p> <p>NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at 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.</p>
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 trial mandated discontinuation of antihypertensive medication, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out in the approved summary of product characteristics (SmPC) for that product. (This trial is not intending to include any unlicensed drugs as participation in another trial is an exclusion criterion therefore all deprescribed medications will have an approved SmPC)

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

## 12.2. Assessment of Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

- **Unrelated** – where an event is not considered to be related to the IMP (discontinuation of antihypertensive medication).
- **Possibly** – although a relationship to the IMP (discontinuation of antihypertensive medication) cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.
- **Probably** – the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP (discontinuation of antihypertensive medication).
- **Definitely** – the known effects of the IMP (discontinuation of antihypertensive medication) or its therapeutic class suggest that the IMP is the most likely cause.

All AEs (SAEs) considered to have a causality category of “possibly”, “probably” or “definitely” will be considered as related to the IMP.

### **12.3. Procedures for Recording Adverse Events**

Adverse Events of interest (listed in appendix F) occurring during the active follow-up period of the trial (1 year from randomisation for each participant), that are observed by the Investigator or reported by the participant or their carer, will be reported on the trial CRF, whether or not attributed to trial medication. As this participant population are at an increased risk of adverse events, those outside the area of interest will not be reported unless deemed related to antihypertensive medication reduction or considered serious, as determined by the GP (or qualified and appropriately trained health professional responsible for hypertension care or medicines management). ADWEs will be captured at the 4 week safety visit/s.

The following information will be reported on the CRF: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary. The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

Non-serious AEs considered related to the trial medication as judged by a medically qualified investigator or the Sponsor will be followed up either until resolution, or the event is considered stable. All related AEs that result in a participant’s withdrawal from the trial or are present at the end of the trial, should be followed up until a satisfactory resolution occurs. It will be left to the recruiting physician’s clinical judgment whether or not an AE is of sufficient severity to require re-introduction of the participant’s withdrawn treatment and the reason will be recorded. A participant may also voluntarily have treatment re-introduced due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

### **12.4. Reporting Procedures for Serious Adverse Events**

All SAEs must be reported on the SAE Reporting Form to the Sponsor or delegate immediately or within 24 hours of Site Trial Team becoming aware of the event being defined as serious (appendix F).

#### **12.4.1. Events exempt from immediate reporting as SAEs**

The following events are exempt from SAE reporting purposes:

- Admission to hospital for routine, planned medical procedures or health assessment (e.g. hip replacement, routine transfusions).
- Admission to hospital or prolongation of hospitalisation for any reason other than for health purposes (e.g. prolongation of hospitalisation while appropriate social care is set up).
- Hospital visits for <24 hours that do not result in in-patient admission, unless considered an important medical event.

In order to ensure that SAE reporting timelines are met, SAEs which also meet trial endpoints will not be exempt from reporting.

#### **12.4.2. Procedure for immediate reporting of Serious Adverse Events**

All SAEs occurring during the safety reporting window (from randomisation to the end of the individual's 12 month follow-up), either observed by the recruiting physician or reported by the participant, whether or not attributed to trial intervention, will be recorded and forwarded by the site to PC-CTU, using the "PC-CTU SAE Report Form" following assessment for seriousness and relatedness by the site clinician. This form will be completed and sent using secure email, to the PC-CTU using the number/email quoted on the report form. As a minimum, the following information will be recorded:

- Participant ID
- Event Name
- Reason event classed as Serious
- Description
- Date of onset
- End date
- Severity
- Assessment of relatedness to reduction of antihypertensive medication
- Other suspect drug or device
- Action taken

SAEs must be reported to the PC-CTU within 24 hours of discovery or notification of the event. The PC-CTU will acknowledge receipt of the SAE Report Form using the PC-CTU 'SAE Form Receipt' document. This receipt will be emailed to the site physician. If the site physician does not receive a receipt within 24hrs of them sending the report (during office hours), they should re-send the SAE Report Form to the PC-CTU by email and telephone ahead.

The documentation will be reviewed by the Trial Management Team and logged on the SAE Tracker and retained by the PC-CTU. Following the initial check of the report, any additional information will be requested, and the CI/Trial Lead or their medically qualified designated representative will review and evaluate the report for seriousness, causality and expectedness. In the event of a SUSAR the reporting timelines stated below will be followed. If there have been two assessments of causality made, the site physician's assessment cannot be downgraded. Where there is a discrepancy the worst case assessment is used for reporting purposes. The PC-CTU will also ensure that a summary of SAE report is reviewed by the DMEC at each meeting during the trial. This arrangement will be reviewed by the DMEC prior to, and during the trial, depending on the expected and observed rate of SAEs.

Additional information, as it becomes available, will also be reported on the SAE Report Form (i.e. updating the original form) and returned to the PC-CTU by email as above. The SAE Report Form will be filed in the Trial Master File according to PC-CTU SOP TM112 'Trial Master File and associated files', with copies filed in the patient's notes, the Case Record Form file and the Investigator Site File.

Trial Managers will complete regular reports which will be reviewed by the senior members of the PC-CTU. One of the metrics contained within this reporting is the number of SAEs reported and the cumulative number of SAEs for each trial. Any concerns identified will be immediately raised with the Chief Investigator/Trial Leads and may be tabled for discussion at the regular PC-CTU Management Committee meetings or referred to the trial's DMEC chair for review. The DMEC also monitors the frequency and pattern of events reported as part of its independent oversight of the trial and will be provided with 6 monthly summaries.

### **12.5. Expectedness**

As there are no sections of the SmPC which detail expected adverse events as a result of medication withdrawal (the study IMP), for SAEs that require reporting, expectedness of SARs will be determined whether or not they have been shown to occur in our previous trial of antihypertensive medication reduction.<sup>22</sup> These will be listed in the IMP dossier. The RSI used (within the SmPC) will be the current Sponsor and MHRA approved version at the time of the event occurrence.

### **12.6. SUSAR Reporting**

All SUSARs will be reported by the sponsor delegate to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARs, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

### **12.7. Development Safety Update Reports**

The CI (or Co-Principal Investigator and Co-Trial Lead if delegated by the CI) will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

## **13. STATISTICS**

### **13.1. Statistical Analysis Plan (SAP)**

The statistical aspects of the trial are summarised here with details fully described in a statistical analysis plan (SAP) that will be available from the time that the first participant is recruited. The SAP will be finalised before any analysis takes place. Cost-effectiveness analyses are described in section 11.

### **13.2. Description of Statistical Methods**

Descriptive summaries of baseline characteristics will be presented by randomised group; neither tests of statistical significance nor confidence intervals for differences between groups will be presented.

The primary analysis will be according to randomised treatment assignment and will include all randomised participants for whom data are available, as defined by protocol eligibility criteria. Deprescribing antihypertensive medication will be deemed non-inferior to usual care in terms of death or emergency hospital admission if the lower limit of the 2-sided 95% confidence interval (CI) for the absolute risk difference (of the percentage of participants experiencing emergency hospitalisation/death) between the usual care and the medication reduction group is above -5% i.e. if the percentage of “failures” in the deprescribing group is less than 5 percentage units higher than in the usual care group. This primary outcome will be analysed using a generalised linear mixed effects model. The response will be a binary indicator of whether the participant experienced death or emergency hospitalisation at 1 year. The model will include age as a fixed effect and site as a random effect. In a sensitivity analysis, any covariates found to be predictive of missingness in the outcome, through fitting univariate logistic regression models, will be included in the model.

Generalised linear models adjusting for age as a fixed effect and site as a random effect will be used for secondary outcomes e.g. differences in the proportions of patients with serious falls, serious hypotension, syncope, fracture, hospitalisation/death, any non-serious adverse event, ADWE, all-cause death, major cardiovascular events, stroke, MI and perceived side effects to antihypertensive at 12 months, differences in mean change in treatment burden score, number of prescribed medications, number of prescribed antihypertensives, blood pressure, quality of life at 12 months. Any supplementary time-to-event analyses for cause-specific hospitalisation/death secondary outcomes will be described in the SAP.

Descriptive summaries of adverse events in the safety population will be presented.

The trial results will be reported in accordance with the CONSORT 2010 statement<sup>53</sup> (and extension for non-inferiority and equivalence trials 2012).<sup>54</sup>

### **13.3. Subgroup and sensitivity analyses**

Pre-specified exploratory subgroup analyses are summarised in section 6. Missing data will be reported and the missing data mechanism explored. Additional sensitivity analysis using imputation methods (e.g. multiple imputation) will be performed if relevant.

### **13.4. Long term follow-up**

If non-inferiority is demonstrated at 1 year, time to death or emergency hospital admission will be examined at around 3 years follow-up using Cox proportional hazards models if assumptions hold, or suitable time to event model alternatives. If further funding is obtained then this will also be examined at 5 and 10 year follow-up points. All other secondary clinical endpoints will be examined at these timepoints, where data are available in electronic health records. A Statistical Analysis Plan for the long-term follow-up will be prepared to provide further details of the different analyses proposed.

### **13.5. Sample Size Determination**

The trial will aim to randomise 3,014 participants and actively follow them up for 1 year to determine whether there is a non-inferior difference in death or first emergency hospital admission between treatment groups. This sample size gives 90% power to demonstrate a non-inferior margin of 5%, at 2.5% 1-sided level of significance, accounting for 5% loss to follow-up.

This is based on a rate of emergency hospital admissions in the usual care group of 20.7% at 12 months, based on previously reported rates from HES data (see table 2 in Hippisley-Cox & Coupland, 2013)<sup>55</sup> inflated by 1% to take into account those people that die without a preceding emergency admission.<sup>56</sup> Due to the efficient trial design being employed, where most outcomes are measured using linked electronic health records, minimal loss to follow-up is expected. However, the sample size does include adjustment for up to 5% loss to follow-up, in the event that patients withdraw completely or records cannot be linked, based on our previous trial (where 1.4% of participants were lost to follow-up).<sup>22</sup>

### **13.6. Analysis Populations**

The primary analysis population will include all eligible randomised participants for whom data are available. Participants will be analysed according to their randomised treatment assignment irrespective of the treatment they actually receive. Participants who withdraw from the trial will be included in the analysis until the point at which they withdraw; data from participants who withdraw from treatment and/or active follow-up only will continue to be included in the analysis as far as the data are available. The population will be used for all primary and secondary analyses unless otherwise specified.

Safety analysis will be undertaken using the “as-treated population”, i.e. this safety population will consist of all participants who stopped taking at least one antihypertensive (regardless of whether they later restarted) versus those who continued taking their prescribed antihypertensives, regardless of their allocated randomisation group.

Other analysis populations to assess the robustness of the results will be described in the SAP.

### **13.7. Decision Points**

The traffic light approach will be used for the assessment of internal pilot objectives after six months of recruitment (Section 9.9). Results will be made available to the trial management and oversight committees. At 12 months, provided the primary outcome is non-inferior to usual care, a decision will be made, together with the Trial Steering Committee [TSC], Data Monitoring and Ethics Committee [DMEC] and funders, to continue to follow-up participants ‘passively’ via electronic health records or via ORCHID with assessment of study outcomes at 3 years, 5 years and 10 years post randomisation (subject to funding).

### **13.8. Stopping Rules**

There will be no safety stopping rules but the DMEC will monitor the safety of the trial. The TSC will recommend to the funder (NIHR HTA) that the trial should be terminated if deemed necessary.

### **13.9. The Level of Statistical Significance**

For the non-inferiority analysis, the level of significance is set at 2.5% (equivalent to a 95% 2-sided CI). For other analyses, a 5% two-sided significance level will be used where appropriate. No adjustments will be made for multiple comparisons.

### **13.10. Procedure for Accounting for Missing, Unused, and Spurious Data.**

Missing data will be reported with reasons given where available, and the missing data pattern will be examined. We will explore the mechanism of missing data by means of logistic regression models which will explore if missingness (i.e. whether the primary outcome is missing or not) is related to measured baseline variables. Covariates found to be predictive of missingness will, where appropriate, be included as a covariate in the analysis model.

### **13.11. Procedures for Reporting any Deviation(s) from the Statistical Plan**

The final statistical analysis plan will be agreed prior to final data lock and prior to any analyses taking place. Any deviation thereafter will be reported in the final trial report.

## **14. DATA MANAGEMENT**

The data management aspects of the trial are summarised here with details fully described in the Data Management Plan.

### **14.1. Source Data**

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, Primary Care and hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, pharmacy records, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data; e.g. baseline clinic blood pressure measurements). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

Original copies of the Consent Form will be securely sent to the central trial team, and a copy kept at site/filed in patients' medical notes. For consent that is taken digitally within REDCap (handwritten signature using a finger or a stylus or biometric eSignatures), the eConsent form will be downloaded and held securely by the central trial team on an access-restricted University of Oxford server. These will be held during and after the end of the trial according to the legally required retention period and made available for inspection where required.

### **14.2. Access to Data**

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. Summary results data will be included on the trial registration database within 12 months of the end of the trial. Requests for data

(anonymised trial participant level data) will only be provided to external researchers who provide a methodologically sound proposal to the trial team (and who will be required to sign a data sharing access agreement with the Sponsor) and/or in accordance with the NIHR's guidance. Participant consent for this is included in the informed consent form.

#### **14.3. Data Recording and Record Keeping**

All manually collected trial data (except specific questionnaires not validated for electronic data capture) will be entered on to electronic CRFs which will link directly to the trial database. This trial intends to use the RedCap eCRF system where data are stored on secure servers with user access and logins controlled by our data manager. In order to ensure patient confidentiality is protected there is an ongoing process of review and improvement in place. Consent will be taken on paper forms in face-to-face visits and copies stored securely with participant notes and in a secure cabinet held by the central trial team. If consent is taken remotely this form will be held in the eCRF system as well as copies held as above. Follow-up data from routine electronic health records will be uploaded directly onto the trial database, linked to participant records via a unique trial identifier.

The clinical database will be built and managed by the PC-CTU in line with the PC-CTU SOPs and will hold and allow data management of all data points required to conduct the final analysis. The clinical database will be built on an externally validated secure web-based platform allowing for data tracking by use of date stamped audit logs. Within this database, participants will be identified only by a unique Trial ID (aside from on any electronic consent forms where name is required) to offer patient confidentiality and protect against bias. A database with restricted access will be used to securely store identifiable patient information required to contact patients and permit long term follow-up in the future. Access to these data will be strictly on a need to know basis and databases will be password protected on a secure server. The identifiers will be held separately from the CRFs collecting clinical data. The unique trial identifier will be generated for every participant enrolled to the trial and this will be entered onto both trial databases to permit linkage of identifiable and anonymised clinical data where necessary. Each database will include secure login for staff at participating sites and facilities for manual entry of data and upload of files where appropriate. A clinical data manager will be assigned to the trial supervised by Oxford PC-CTU's Senior Data Manager and PC-CTU SOPs will be followed.

All data will be stored within these databases until all analyses have been completed, in compliance with the University of Oxford standard operating procedures for data retention. On completion of the trial and data cleaning, the trial documentation will be transferred to a secure, GCP compliant archiving facility, where they will be held for at least 5 years. Contact information will be held for 12 months – 3 years in order to notify participants of the publications of results, after which this will be destroyed. Prior to any database lock, the Data Manager and the Trial Statistician will undertake a dataset review as specified in the DMP. Identifiable personal data will be transferred securely using an appropriately secure communications procedures specified in the University of Oxford's *Information Security Handling Rules* (<https://www.infosec.ox.ac.uk/asset-management>)

### **15. QUALITY ASSURANCE PROCEDURES**

#### **15.1. Risk assessment**

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. A risk assessment and monitoring plan was prepared before the trial opened and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

## **15.2. Monitoring**

Regular monitoring will be performed according to GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

The OPTIMISE2 Trial Management Group will be responsible for the monitoring of all aspects of the trial's conduct and progress and will ensure that the protocol is adhered to and that appropriate action is taken to safeguard participants and the quality of the trial itself. The TMG will be comprised of individuals responsible for the trial's day to day management (e.g. the CI/Trial Leads, trial manager, statistician, data manager) and will meet at least monthly throughout the course of the trial.

## **15.3. Trial committees**

### **15.3.1. Trial Steering Committee (TSC)**

A trial steering committee (TSC) will be convened at 6 month intervals to provide overall supervision of the trial and ensure its conduct is in accordance with the principles of GCP and the relevant regulations. The TSC will agree the trial protocol and any protocol amendments and provide advice to the investigators on all aspects of the trial. The TSC will include at least 75% of members who are independent of the investigators, including an independent chairperson. The TSC will have a 'stop guideline' authority to advise early termination of the trial in the event of safety concerns or futility such as poor recruitment rates.

### **15.3.2. Data Monitoring and Ethics Committee (DMEC)**

An independent Data Monitoring and Ethics Committee will meet at 6 monthly intervals before, during and until the end of the trial. The DMEC will include two physicians and a statistician. They will report to and advise the TSC and thus the TMG. The responsibilities of the DMEC and TSC committees are:

- To safeguard the safety, rights and well-being of the trial participants.
- To systematically monitor the trial data and review any analysis as outlined in the Statistical Analysis Plan or as requested by the TSC.
- To evaluate the risk of the trial continuing and take appropriate action where necessary.
- To consider data emerging from other related studies and its potential impact on the trial, if requested by the TSC.
- To pick up any trends, such as increases in un/expected events, and take appropriate action.
- To seek additional advice or information from investigators where required.
- To act or advise, through the Chairman or other consultant, on incidents occurring between meetings that require rapid assessment.

They will review the accruing trial and safety data to ensure trial site staff and participants are aware of any relevant safety information and to determine whether any reasons exist for the trial to be discontinued.

## **16. PROTOCOL DEVIATIONS**

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the trial master file. Where required, sites will be asked to provide details of corrective and preventative actions.

The investigator is not allowed to deviate from the protocol except in the case of an urgent safety measure to protect clinical trial participants from any immediate hazard to their health and safety, in which case such deviations shall be documented and reported to PC-CTU **as soon as possible**.

## **17. SERIOUS BREACHES**

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect 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".

Investigators must notify the trial team **within 1 working day** of identification if a serious breach is suspected. In the event that a serious breach is suspected the Sponsor must be contacted **within 1 working day**. In collaboration with the CI/Trial Lead, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the Research Ethics Committee, Regulatory authority and the relevant NHS host organisation within seven calendar days.

## **18. ETHICAL AND REGULATORY CONSIDERATIONS**

### **18.1. Declaration of Helsinki**

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

### **18.2. Guidelines for Good Clinical Practice**

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

### **18.3. Approvals**

Following Sponsor approval, the trial documentation (e.g. the protocol, informed consent form, participant information sheet, and any proposed advertising materials) will be submitted to an appropriate Research Ethics Committee (REC), Health Research Authority (HRA) and regulatory authorities (Medicines and Healthcare Regulatory Agency [MHRA]) and host institution(s) for written approval. The trial will be given the identification number REC Ref, Integrated Research Application System (IRAS) ID and ISRCTN number. The trial will be approved by the UK Competent Authority, the MHRA, as it is classified as a clinical trial of an investigational medicinal product (CTIMP). The trial will be conducted in compliance with the approved protocol and standard operating procedures (SOPs), the Declaration of Helsinki, the principles of Good Clinical Practice (GCP), the UK Data Protection Act 2018 and all other applicable regulatory and governance frameworks including the UK policy framework for health and social care research.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

#### **18.4. Other Ethical Considerations**

The trial will aim to include vulnerable individuals with dementia and those lacking capacity to give informed consent and in these instances, consent from an appropriate Personal Legal Representative will be sought. A Personal Legal Representative is defined under the Clinical Trials Regulations and is an individual not connected with the conduct of the trial who is suitable to act as the legal representative by virtue of their relationship with the adult, and is available and willing to do so, and may provide consent to trial inclusion if the patient lacks capacity to consent to participate. Patients lacking capacity to give informed consent and without a Personal Legal Representative present at the point of screening and consent will not be eligible, but they will be invited to attend another baseline appointment if this can be booked with a Personal Legal Representative in attendance.

Cognitive questionnaires will be used in this study which may cause some upset if the participants are unable to complete certain sections. We will have trial staff available either in person or via telephone in order to assist with the completion of these questionnaires and reassure participants.

#### **18.5. Reporting**

The CI (or Co-Principal Investigator and Co-Trial Lead if delegated by the CI) shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

#### **18.6. Transparency in Research**

Prior to the recruitment of the first participant, the trial will be registered on the ISRCTN registry. The trial information will be kept up to date during the trial, and the CI/Trial Lead or their delegate will upload results to all those public registries within 12 months of the end of the trial date, as specified on the end of trial declaration.

#### **18.7. Participant Confidentiality**

The trial will comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant trial number only on all trial documents and any electronic database(s) (excluding consent forms). All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial staff will safeguard the privacy of participants' personal data.

### **18.8. Expenses and Benefits**

Participants will not be paid for participation in this trial and expenses will not be reimbursed.

## **19. FINANCE AND INSURANCE**

### **19.1. Funding**

Research funding is provided by the National Institute for Health and Care Research Health Technology Assessment Programme (NIHR HTA).

### **19.2. Insurance**

The University of Oxford has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment with which participants are provided.

### **19.3. Contractual arrangements**

Appropriate contractual arrangements will be put in place with all third parties.

## **20. PUBLICATION POLICY**

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the trial. Authors will acknowledge that the trial was funded by NIHR HTA in all publications. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

## **21. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY**

Ownership of IP generated by employees of the University of Oxford vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

## **22. ARCHIVING**

Archiving will be done according to PC-CTU SOP and trial specific working instructions. Research documents with personal information, such as consent forms (including paper copies of electronic

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consent), will be held securely at the University of Oxford's archiving facility according to the PC-CTU Archiving SOP. Electronic files will also be stored securely according to the PC-CTU Archiving SOP.

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**24. APPENDIX A: ICD-10/11 codes for defining disease specific trial outcomes**

Condition	ICD- 10 code	Description	ICD- 11 code	Description
Cardiovascular death	IX	Diseases of the circulatory system	BE2Z	Diseases of the circulatory system, unspecified
Myocardial infarction	I21	Acute myocardial infarction	BA41.Z	Acute myocardial infarction, unspecified
	I21.0	Acute transmural myocardial infarction of anterior wall	BA41.Z	Acute myocardial infarction, unspecified
	I21.1	Acute transmural myocardial infarction of inferior wall	BA41.Z	Acute myocardial infarction, unspecified
	I21.2	Acute transmural myocardial infarction of other sites	BA41.Z	Acute myocardial infarction, unspecified
	I21.3	Acute transmural myocardial infarction of unspecified site	BA41.Z	Acute myocardial infarction, unspecified
	I21.4	Acute subendocardial myocardial infarction	BA41.Z	Acute myocardial infarction, unspecified
	I21.9	Acute myocardial infarction, unspecified	BA41.Z	Acute myocardial infarction, unspecified
	I22	Subsequent myocardial infarction	BA42.Z	Subsequent myocardial infarction, unspecified
	I22.0	Subsequent myocardial infarction of anterior wall	BA42.Z	Subsequent myocardial infarction, unspecified
	I22.1	Subsequent myocardial infarction of inferior wall	BA42.Z	Subsequent myocardial infarction, unspecified
	I22.8	Subsequent myocardial infarction of other sites	BA42.Z	Subsequent myocardial infarction, unspecified
	I22.9	Subsequent myocardial infarction of unspecified site	BA42.Z	Subsequent myocardial infarction, unspecified
	I24	Other acute ischaemic heart diseases	BA4Z	Acute ischaemic heart disease, unspecified
Heart Failure	I24.8	Other forms of acute ischaemic heart disease	BA4Z	Acute ischaemic heart disease, unspecified
	I24.9	Acute ischaemic heart disease, unspecified	BA4Z	Acute ischaemic heart disease, unspecified
	I50	Heart failure	BD1Z	Heart failure, unspecified
	I50.0	Congestive heart failure	BD10	Congestive heart failure
	I50.1	Left ventricular failure	BD11.Z	Left ventricular failure, unspecified
	I50.9	Heart failure, unspecified	BD1Z	Heart failure, unspecified
Stroke	I60	Subarachnoid haemorrhage	8B01	Subarachnoid haemorrhage

	I60.0	Subarachnoid haemorrhage from carotid siphon and bifurcation	8B01.0	Aneurysmal subarachnoid haemorrhage
	I60.1	Subarachnoid haemorrhage from middle cerebral artery	8B01.0	Aneurysmal subarachnoid haemorrhage
	I60.2	Subarachnoid haemorrhage from anterior communicating artery	8B01.0	Aneurysmal subarachnoid haemorrhage
	I60.3	Subarachnoid haemorrhage from posterior communicating artery	8B01.0	Aneurysmal subarachnoid haemorrhage
	I60.4	Subarachnoid haemorrhage from basilar artery	8B01.0	Aneurysmal subarachnoid haemorrhage
	I60.5	Subarachnoid haemorrhage from vertebral artery	8B01.0	Aneurysmal subarachnoid haemorrhage
	I60.6	Subarachnoid haemorrhage from other intracranial arteries	8B01.0	Aneurysmal subarachnoid haemorrhage
	I60.7	Subarachnoid haemorrhage from intracranial artery, unspecified	8B01.0	Aneurysmal subarachnoid haemorrhage
	I60.8	Other subarachnoid haemorrhage	8B01	Subarachnoid haemorrhage
	I60.9	Subarachnoid haemorrhage, unspecified	8B01	Subarachnoid haemorrhage
	I61	Intracerebral haemorrhage	8B00.Z	Intracerebral haemorrhage, site unspecified
	I61.0	Intracerebral haemorrhage in hemisphere, subcortical	8B00.0	Deep hemispheric haemorrhage
	I61.1	Intracerebral haemorrhage in hemisphere, cortical	8B00.1	Lobar haemorrhage
	I61.2	Intracerebral haemorrhage in hemisphere, unspecified	8B00.Z	Intracerebral haemorrhage, site unspecified
	I61.3	Intracerebral haemorrhage in brain stem	8B00.2	Brainstem haemorrhage
	I61.4	Intracerebral haemorrhage in cerebellum	8B00.3	Cerebellar haemorrhage
	I61.5	Intracerebral haemorrhage, intraventricular	8B00.4	Intraventricular haemorrhage without parenchymal haemorrhage
	I61.6	Intracerebral haemorrhage, multiple localized	8B00.5	Haemorrhage of multiple sites
	I61.8	Other intracerebral haemorrhage	8B00.Z	Intracerebral haemorrhage, site unspecified
	I61.9	Intracerebral haemorrhage, unspecified	8B00.Z	Intracerebral haemorrhage, site unspecified
	I62	Other nontraumatic intracranial haemorrhage	8B0Z	Intracranial haemorrhage, unspecified

	I62.9	Intracranial haemorrhage (nontraumatic), unspecified	8B0Z	Intracranial haemorrhage, unspecified
	I63	Cerebral infarction	8B11	Cerebral ischaemic stroke
	I63.0	Cerebral infarction due to thrombosis of precerebral arteries	8B11.0	Cerebral ischaemic stroke due to extracranial large artery atherosclerosis
	I63.1	Cerebral infarction due to embolism of precerebral arteries	8B11.2Z	Cerebral ischaemic stroke due to embolic occlusion, unspecified
	I63.2	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries	8B11.50	Cerebral ischaemic stroke due to unspecified occlusion or stenosis of extracranial large artery
	I63.3	Cerebral infarction due to thrombosis of cerebral arteries	8B11.1	Cerebral ischaemic stroke due to intracranial large artery atherosclerosis
	I63.4	Cerebral infarction due to embolism of cerebral arteries	8B11.2Z	Cerebral ischaemic stroke due to embolic occlusion, unspecified
	I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries	8B11.51	Cerebral ischaemic stroke due to unspecified occlusion or stenosis of intracranial large artery
	I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic	8B11	Cerebral ischaemic stroke
	I63.8	Other cerebral infarction	8B11	Cerebral ischaemic stroke
	I63.9	Cerebral infarction, unspecified	8B11	Cerebral ischaemic stroke
	I64	Stroke, not specified as haemorrhage or infarction	8B20	Stroke not known if ischaemic or haemorrhagic
Hypotension	I95	Hypotension	BA2Z	Hypotension, unspecified
	I95.0	Idiopathic hypotension	BA20	Idiopathic hypotension
	I95.1	Orthostatic hypotension	BA21	Orthostatic hypotension
	I95.2	Hypotension due to drugs	BA2Z	Hypotension, unspecified
	I95.8	Other hypotension	BA2Z	Hypotension, unspecified
	I95.9	Hypotension, unspecified	BA2Z	Hypotension, unspecified
Syncope	R55	Syncope and collapse	MG45.Z	Syncope and collapse, unspecified
Fracture	S02	Fracture of skull and facial bones	NA02.Z	Fracture of skull and facial bones, part unspecified
	S02.0	Fracture of vault of skull	NA02.0	Fracture of vault of skull
	S02.1	Fracture of base of skull	NA02.1Z	Fracture of base of skull, unspecified
	S02.2	Fracture of nasal bones	NA02.3	Fracture of nasal bones

S02.3	Fracture of orbital floor	NA02.21	Fracture of orbital floor
S02.4	Fracture of malar and maxillary bones	NA02.4Z	Fracture of maxilla, unspecified
S02.5	Fracture of tooth	NA02.Z	Fracture of skull and facial bones, part unspecified
S02.6	Fracture of mandible	NA02.7Z	Fracture of mandible, unspecified
S02.7	Multiple fractures involving skull and facial bones	NA02.8	Multiple fractures involving skull or facial bones
S02.8	Fractures of other skull and facial bones	NA02.Z	Fracture of skull and facial bones, part unspecified
S02.9	Fracture of skull and facial bones, part unspecified	NA02.Z	Fracture of skull and facial bones, part unspecified
S12	Fracture of neck	NA22.Z	Fracture of neck, unspecified
S12.0	Fracture of first cervical vertebra	NA22.0Z	Fracture of first cervical vertebra, unspecified
S12.1	Fracture of second cervical vertebra	NA22.1Z	Fracture of second cervical vertebra, unspecified
S12.2	Fracture of other specified cervical vertebra	NA22.Z	Fracture of neck, unspecified
S12.7	Multiple fractures of cervical spine	NA22.3	Multiple fractures of cervical spine
S12.8	Fracture of other parts of neck	NA22.Z	Fracture of neck, unspecified
S12.9	Fracture of neck, part unspecified	NA22.Z	Fracture of neck, unspecified
S22	Fracture of rib(s), sternum and thoracic spine	NA82.Z	Fracture of rib, sternum or thoracic spine, unspecified
S22.0	Fracture of thoracic vertebra	NA82.0	Fracture of thoracic vertebra
S22.1	Multiple fractures of thoracic spine	NA82.1	Multiple fractures of thoracic spine
S22.2	Fracture of sternum	NA82.2	Fracture of sternum
S22.3	Fracture of rib	NA82.3Z	Fracture of rib, unspecified
S22.4	Multiple fractures of ribs	NA82.4	Multiple fractures of ribs
S22.5	Flail chest	NA82.5	Flail chest
S22.8	Fracture of other parts of bony thorax	NA82.Z	Fracture of rib, sternum or thoracic spine, unspecified
S22.9	Fracture of bony thorax, part unspecified	NA82.Z	Fracture of rib, sternum or thoracic spine, unspecified
S32	Fracture of lumbar spine and pelvis	NB52.Z	Fracture of lumbar spine or pelvis, unspecified
S32.0	Fracture of lumbar vertebra	NB52.0	Fracture of lumbar vertebra
S32.1	Fracture of sacrum	NB52.10	Fracture of sacrum without disruption of pelvic ring
S32.2	Fracture of coccyx	NB52.11	Fracture of coccyx
S32.3	Fracture of ilium	NB52.12	Fracture of ilium without disruption of pelvic ring

	S32.4	Fracture of acetabulum	NB52.13	Fracture of acetabulum without disruption of pelvic ring
	S32.5	Fracture of pubis	NB52.14	Fracture of pubis without disruption of pelvic ring
	S32.7	Multiple fractures of lumbar spine and pelvis	NB52.4	Multiple fractures of lumbar spine or pelvis
	S32.8	Fracture of other and unspecified parts of lumbar spine and pelvis	NB52.Z	Fracture of lumbar spine or pelvis, unspecified
	S42	Fracture of shoulder and upper arm	NC12.Z	Fracture of shoulder or upper arm, unspecified
	S42.0	Fracture of clavicle	NC12.0Z	Fracture of clavicle, unspecified
	S42.1	Fracture of scapula	NC12.1Z	Fracture of scapula, unspecified
	S42.2	Fracture of upper end of humerus	NC12.2Z	Fracture of upper end of humerus, unspecified site
	S42.3	Fracture of shaft of humerus	NC12.3	Fracture of shaft of humerus
	S42.4	Fracture of lower end of humerus	NC12.4Z	Fracture of lower end of humerus, unspecified
	S42.7	Multiple fractures of clavicle, scapula and humerus	NC12.5	Multiple fractures of clavicle, scapula or humerus
	S42.8	Fracture of other parts of shoulder and upper arm	NC12.6	Fracture of other parts of shoulder or upper arm
	S42.9	Fracture of shoulder girdle, part unspecified	NC12.7	Fracture of shoulder girdle, part unspecified
	S52	Fracture of forearm	NC32.Z	Fracture of forearm, unspecified
	S52.0	Fracture of upper end of ulna	NC32.0	Fracture of upper end of ulna
	S52.1	Fracture of upper end of radius	NC32.1	Fracture of upper end of radius
	S52.2	Fracture of shaft of ulna	NC32.2	Fracture of shaft of ulna
	S52.3	Fracture of shaft of radius	NC32.3	Fracture of shaft of radius
	S52.4	Fracture of shafts of both ulna and radius	NC32.4	Fracture of shafts of both ulna and radius
	S52.5	Fracture of lower end of radius	NC32.5Z	Fracture of lower end of radius, unspecified
	S52.6	Fracture of lower end of both ulna and radius	NC32.6	Fracture of lower end of both ulna and radius
	S52.7	Multiple fractures of forearm	NC32.7	Multiple fractures of forearm
	S52.8	Fracture of other parts of forearm	NC32.Z	Fracture of forearm, unspecified
	S52.9	Fracture of forearm, part unspecified	NC32.Z	Fracture of forearm, unspecified
	S62	Fracture at wrist and hand level	NC53.Z	Fracture at wrist or hand level, unspecified
	S62.0	Fracture of navicular [scaphoid] bone of hand	NC53.0	Fracture of scaphoid bone of hand
	S62.1	Fracture of other carpal bone(s)	NC53.1	Fracture of other carpal bone

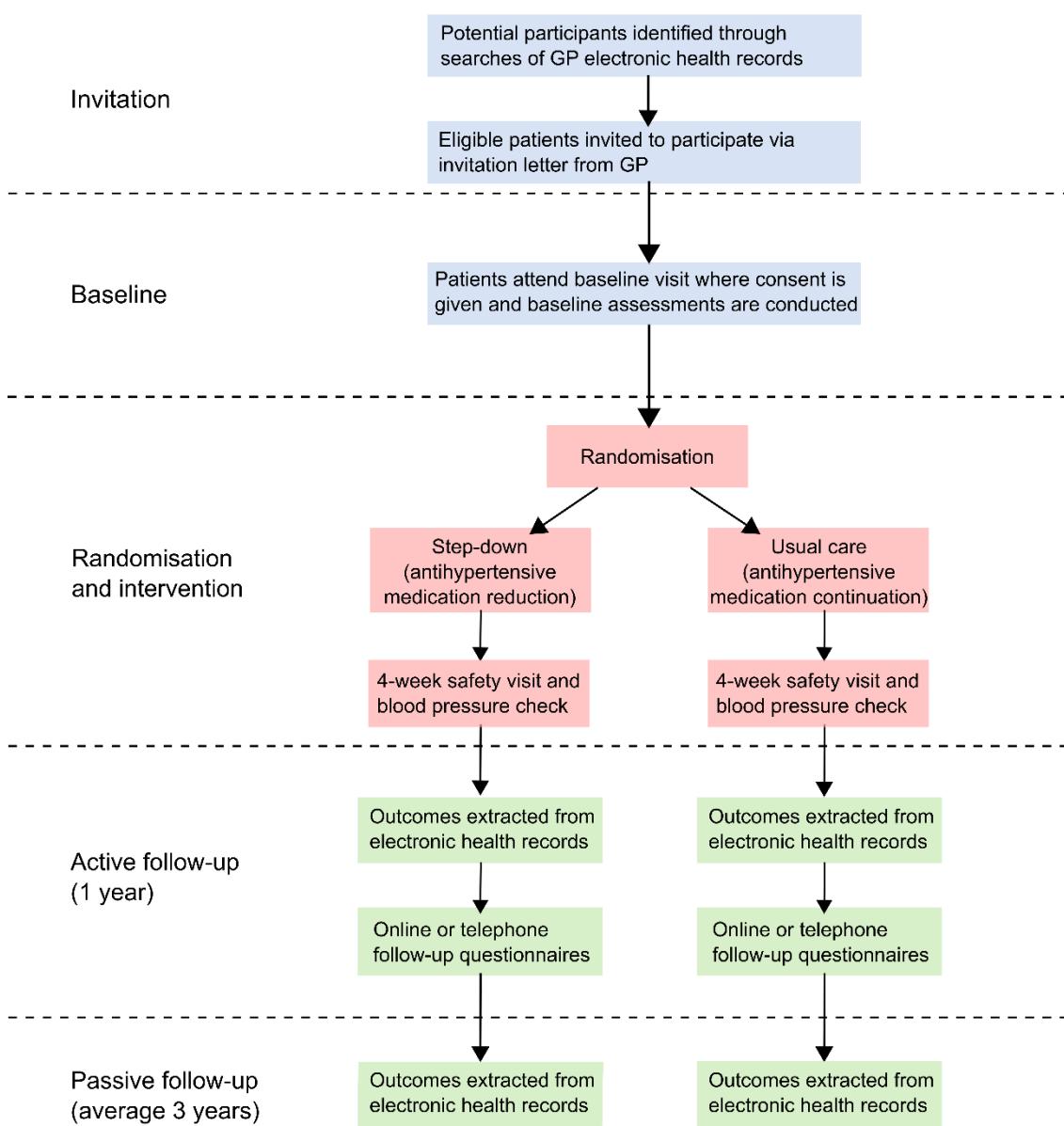
S62.2	Fracture of first metacarpal bone	NC53.2	Fracture of first metacarpal bone
S62.3	Fracture of other metacarpal bone	NC53.3Z	Fracture of other metacarpal bone, unspecified
S62.4	Multiple fractures of metacarpal bones	NC53.4	Multiple fractures of metacarpal bones
S62.5	Fracture of thumb	NC53.5	Fracture of thumb bone
S62.6	Fracture of other finger	NC53.6Z	Fracture of other finger bone, unspecified
S62.7	Multiple fractures of fingers	NC53.7	Multiple fractures of fingers
S62.8	Fracture of other and unspecified parts of wrist and hand	NC53.Z	Fracture at wrist or hand level, unspecified
S72	Fracture of femur	NC72.Z	Fracture of femur, unspecified
S72.0	Fracture of neck of femur	NC72.2Z	Fracture of neck of femur, unspecified
S72.1	Petrochanteric fracture	NC72.3Z	Fracture of unspecified trochanteric section of femur
S72.2	Subtrochanteric fracture	NC72.4	Subtrochanteric fracture of femur
S72.3	Fracture of shaft of femur	NC72.5	Fracture of shaft of femur
S72.4	Fracture of lower end of femur	NC72.6Z	Fracture of lower end of femur, unspecified
S72.7	Multiple fractures of femur	NC72.7	Multiple fractures of femur
S72.8	Fractures of other parts of femur	NC72.8	Fractures of other parts of femur
S72.9	Fracture of femur, part unspecified	NC72.Z	Fracture of femur, unspecified
S82	Fracture of lower leg, including ankle	NC92.Z	Fracture of lower leg, including ankle, unspecified
S82.0	Fracture of patella	NC92.0	Fracture of patella
S82.1	Fracture of upper end of tibia	NC92.1Z	Fracture of upper end of tibia, unspecified
S82.2	Fracture of shaft of tibia	NC92.2	Fracture of shaft of tibia
S82.3	Fracture of lower end of tibia	NC92.3	Fracture of lower end of tibia
S82.4	Fracture of fibula alone	NC92.4Z	Fracture of fibula alone, unspecified
S82.5	Fracture of medial malleolus	NC92.5	Fracture of medial malleolus
S82.6	Fracture of lateral malleolus	NC92.6	Fracture of lateral malleolus
S82.7	Multiple fractures of lower leg	NC92.8	Multiple fractures of lower leg
S82.8	Fractures of other parts of lower leg	NC92.Z	Fracture of lower leg, including ankle, unspecified
S82.9	Fracture of lower leg, part unspecified	NC92.Z	Fracture of lower leg, including ankle, unspecified
S92	Fracture of foot, except ankle	ND13.Z	Fracture of foot, except ankle, unspecified
S92.0	Fracture of calcaneus	ND13.0	Fracture of calcaneus

S92.1	Fracture of talus	ND13.1	Fracture of talus	
S92.2	Fracture of other tarsal bone(s)	ND13.2	Fracture of unspecified tarsal bone	
S92.3	Fracture of metatarsal bone	ND13.3	Fracture of metatarsal bone	
S92.4	Fracture of great toe	ND13.4	Fracture of great toe	
S92.5	Fracture of other toe	ND13.5	Fracture of other toe	
S92.7	Multiple fractures of foot	ND13.6	Multiple fractures of foot	
S92.9	Fracture of foot, unspecified	ND13.Z	Fracture of foot, except ankle, unspecified	
T02	Fractures involving multiple body regions	ND32	Fractures involving multiple body regions	
T02.0	Fractures involving head with neck	ND32	Fractures involving multiple body regions	
T02.1	Fractures involving thorax with lower back and pelvis	ND32	Fractures involving multiple body regions	
T02.2	Fractures involving multiple regions of one upper limb	ND32	Fractures involving multiple body regions	
T02.3	Fractures involving multiple regions of one lower limb	ND32	Fractures involving multiple body regions	
T02.4	Fractures involving multiple regions of both upper limbs	ND32	Fractures involving multiple body regions	
T02.5	Fractures involving multiple regions of both lower limbs	ND32	Fractures involving multiple body regions	
T02.6	Fractures involving multiple regions of upper limb(s) with lower limb(s)	ND32	Fractures involving multiple body regions	
T02.7	Fractures involving thorax with lower back and pelvis with limb(s)	ND32	Fractures involving multiple body regions	
T02.8	Fractures involving other combinations of body regions	ND32	Fractures involving multiple body regions	
T02.9	Multiple fractures, unspecified	ND32	Fractures involving multiple body regions	
T08	Fracture of spine, level unspecified	ND50	Fracture of spine, level unspecified	
T10	Fracture of upper limb, level unspecified	ND52	Fracture of arm, level unspecified	
T12	Fracture of lower limb, level unspecified	ND54	Fracture of leg, level unspecified	
T14.2	Fracture of unspecified body region	ND56.2	Fracture of unspecified body region	
Fall	W01	Fall on same level from slipping, tripping and stumbling	PA60&XE78X	Unintentional fall on the same level or from less than 1 metre / Bathtub

	W05	Fall involving wheelchair	PA60&XE293	Unintentional fall on the same level or from less than 1 metre / Wheelchair
	W06	Fall involving bed	PA60&XE8PK	Unintentional fall on the same level or from less than 1 metre / Bed, bedding or bedding accessories
	W07	Fall involving chair	PA60&XE769	Unintentional fall on the same level or from less than 1 metre / Chair or sofa
	W08	Fall involving other furniture	PA60&XE5HA	Unintentional fall on the same level or from less than 1 metre / Furniture or furnishing
	W10	Fall on and from stairs and steps	PA60&XE3HC	Unintentional fall on the same level or from less than 1 metre / Stairs, steps
	W17	Other fall from one level to another	PA6Z	Unintentional fall from unspecified height
	W18	Other fall on same level	PA60	Unintentional fall on the same level or from less than 1 metre
	W19	Unspecified fall	PA6Z	Unintentional fall from unspecified height
Dementia	F00	Dementia in Alzheimer disease	6D80.Z	Dementia due to Alzheimer disease, onset unknown or unspecified
	F00.0	Dementia in Alzheimer disease with early onset	6D80.0	Dementia due to Alzheimer disease with early onset
	F00.1	Dementia in Alzheimer disease with late onset	6D80.1	Dementia due to Alzheimer disease with late onset
	F00.2	Dementia in Alzheimer disease, atypical or mixed type	6D80.Z	Dementia due to Alzheimer disease, onset unknown or unspecified
	F00.9	Dementia in Alzheimer disease, unspecified	6D80.Z	Dementia due to Alzheimer disease, onset unknown or unspecified
	F01	Vascular dementia	6D81	Dementia due to cerebrovascular disease
	F01.0	Vascular dementia of acute onset	6D81	Dementia due to cerebrovascular disease
	F01.1	Multi-infarct dementia	6D81	Dementia due to cerebrovascular disease
	F01.2	Subcortical vascular dementia	6D81	Dementia due to cerebrovascular disease
	F01.3	Mixed cortical and subcortical vascular dementia	6D81	Dementia due to cerebrovascular disease
	F01.8	Other vascular dementia	6D81	Dementia due to cerebrovascular disease
	F01.9	Vascular dementia, unspecified	6D81	Dementia due to cerebrovascular disease
	F02	Dementia in other diseases classified elsewhere	6D8Z	Dementia, unknown or unspecified cause

	F02.0	Dementia in Pick disease	6D83	Frontotemporal dementia
	F02.1	Dementia in Creutzfeldt-Jakob disease	6D85.5	Dementia due to prion disease
	F02.2	Dementia in Huntington disease	6D85.1	Dementia due to Huntington disease
	F02.3	Dementia in Parkinson disease	6D85.0	Dementia due to Parkinson disease
	F02.4	Dementia in human immunodeficiency virus [HIV] disease	6D85.3	Dementia due to human immunodeficiency virus
	F02.8	Dementia in other specified diseases classified elsewhere	6D8Z	Dementia, unknown or unspecified cause
	F03	Unspecified dementia	6D8Z	Dementia, unknown or unspecified cause

## 25. APPENDIX B: Trial flow chart



GP = General practitioner

Note: The 4 week safety visit will be repeated each time a medication is withdrawn.

## 26. APPENDIX C: Schedule of procedures

Procedures	Variables	Visits			Data sources			
		Visit 1 Day 0 Baseline	Visit 2* Day 28 Safety visit	Day 365 Follow-up	Manual data entry	Questionnaire**	Primary care record	Secondary Care record
		In-person/remote	In-person	Remote	In-person	In-person/remote	Remote	Remote
Baseline procedures	Informed consent	x			x			
	Eligibility assessment	x			x			
	Randomisation	x			x			
Demographics	Age	x			x			
	Date of Birth	x			x			
	Postcode	x			x			
	Gender Assigned at Birth	x			x			
	Gender Identity	x			x			
	Ethnicity	x			x			
	Registered disability	x			x			
	Sexual orientation	x			x			
	Religion	x			x			
	Marital status	x			x			
	Education	x			x			
	Duration of hypertension	x			x			
	Alcohol consumption ****	x			x	x	x	
	Smoking status ****	x			x	x	x	
	Height	x			x			
	Weight	x			x			
	Blood pressure - sitting	x	x	x	x		x	
	Blood pressure – standing	x						

	Cholesterol (Total / HDL)	x			x			
	Prescribed medications	x		x	x		x	
<b>Previous medical history</b>	Current/past medical conditions	x			x			
	Cambridge multimorbidity score <sup>57</sup>	x			x			
<b>Frailty assessments</b>	Electronic frailty index <sup>41</sup>	x			x			
<b>Patient reported measures</b>	Multimorbidity Treatment Burden Questionnaire <sup>59</sup>	x		x		x		
	Free-Cog / Tele-Free-Cog <sup>60</sup>	x				x		
	EQ-5D-5L <sup>35</sup>	x		x		x		
	Basic Activities of Daily Living questionnaire ***	x		x		x		
	Symptoms based on the revised illness perception questionnaire <sup>34</sup>	x	x	x		x		
	Beliefs about medicines - general questionnaire <sup>61 ****</sup>	x				x		
	Revised Patient Attitudes Towards Deprescribing questionnaire <sup>62 ****</sup>	x				x		
	Client service receipt inventory ****	x		x		x		
<b>Outcome data</b>	ICD-10/11 coded clinical events							x
	Adverse drug withdrawal events		x	x			x	x
	Admission to a nursing home/long-term care facility					x	x	
	Adverse events		x	x			x	x

\* This visit will be repeated for those in the intervention group if further medications are removed

\*\*Questionnaire follow-up data will be included so long as it is collected/available within - 2/+12 weeks of the scheduled date of follow-up (1 year post-randomisation)

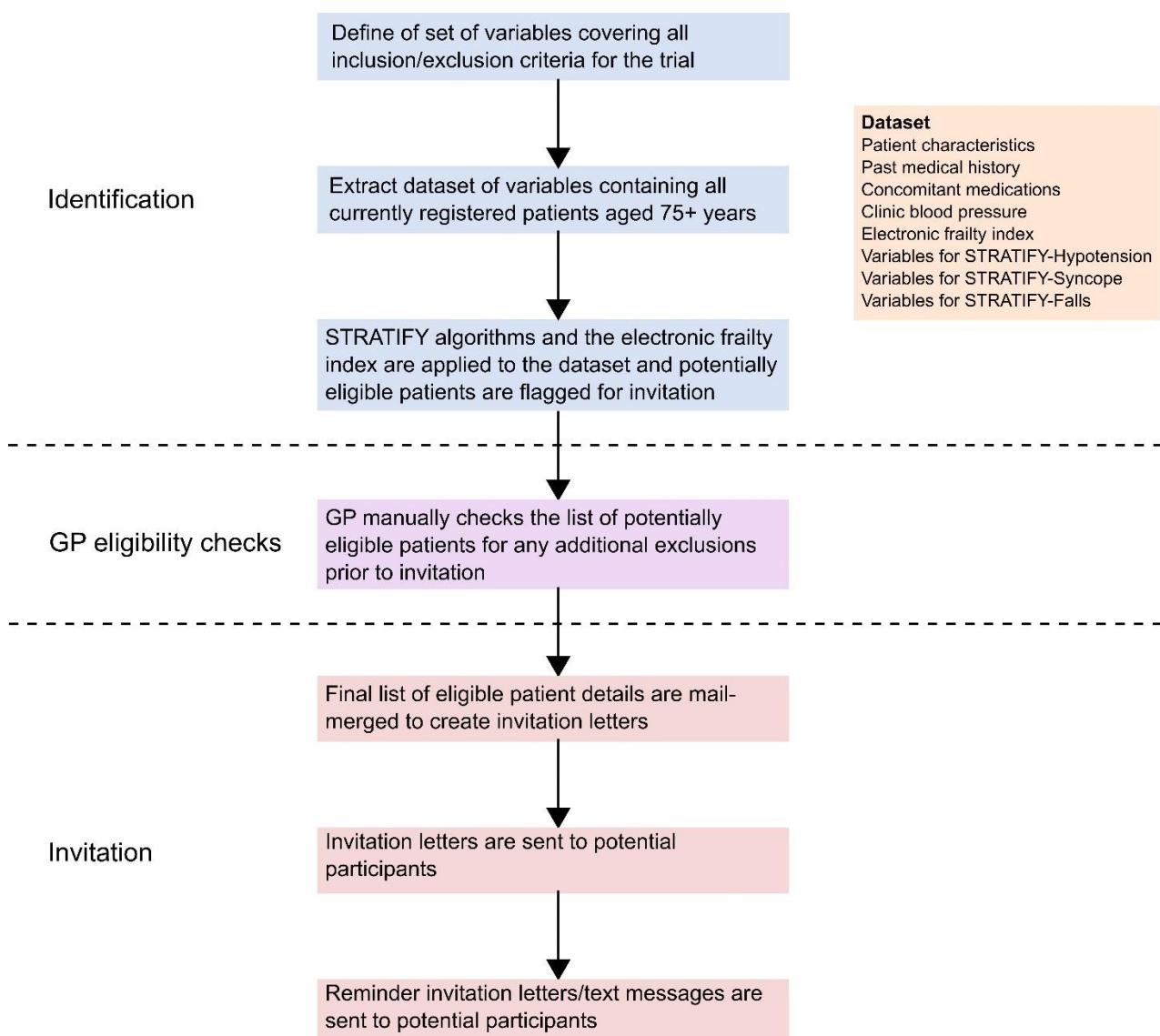
\*\*\* This is based on the Katz Activities of Daily Living score<sup>36</sup> and taken from the Life Ability Questionnaire<sup>58</sup>

\*\*\*\* Alcohol consumption & Smoking status, Beliefs about medicines, Attitudes towards Deprescribing, and the Client Service Receipt Inventory sections of the baseline questionnaire may be provided to the participant on paper for completion following the baseline visit and subsequent entry into the database by a member of the trial team

**27. APPENDIX D: Variables included in the STRATIFY clinical prediction rules**

Category	Variable	STRATIFY-Hypotension	STRATIFY-Syncope	STRATIFY-Falls
Patient characteristics	Age	x	x	x
	Sex	x	x	x
	Ethnicity		x	x
	Body mass index			
	Socioeconomic deprivation	x	x	x
	Smoking	x		x
	Alcohol intake	x	x	x
	Systolic blood pressure	x		
	Total cholesterol			x
	Frailty			x
Medical history	Dizziness	x	x	
	Memory issues			x
	Mobility issues			x
	Dementia		x	
	Multiple sclerosis			x
	Hypotension	x	x	
	Syncope	x	x	
	Falls	x	x	x
	Stroke	x	x	x
	Heart failure		x	
	Chronic kidney disease	x		
	Anaemia	x		
	Atrial Fibrillation	x	x	
	Ischaemic heart disease	x	x	
	Diabetes	x	x	
	Parkinsonism	x	x	
	Bradycardia	x	x	
	Tachycardia	x	x	
	Structural cardiac disease	x	x	
	Cardiopulmonary disease	x	x	
Prescribed medications	ACE inhibitors	x	x	x
	Angiotensin II receptor blockers	x	x	x
	Alpha blockers	x	x	x
	Beta blockers	x	x	x
	Calcium channel blockers	x	x	x
	Diuretics	x	x	x
	Other antihypertensives	x	x	x
	Anticholinergics			x
	Antidepressants	x	x	x
	Hypnotics, anxiolytics	x	x	x
	Opioids	x	x	x
	Antipsychotics		x	

## 28. APPENDIX E: Process of participant identification and invitation



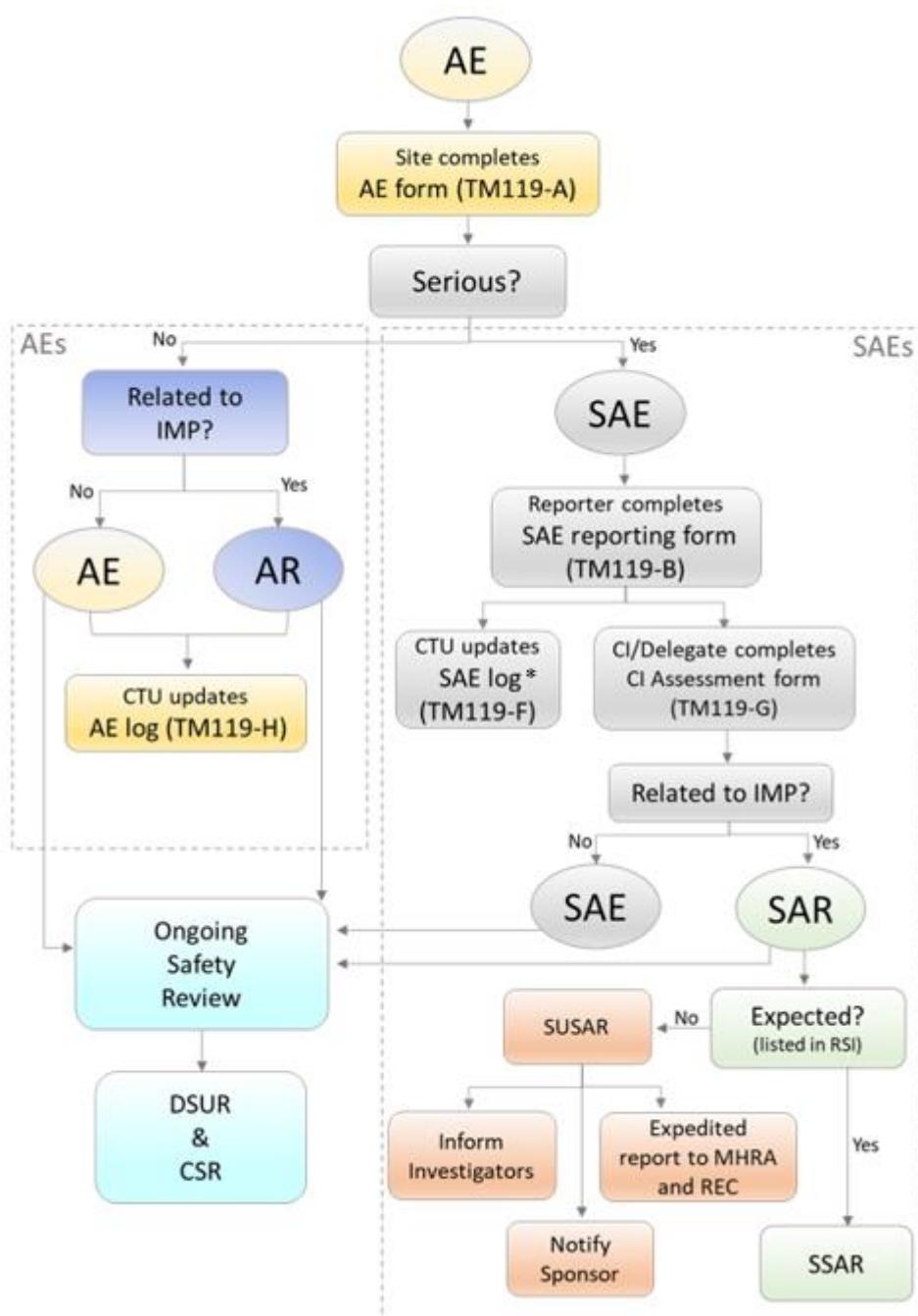
## 29. APPENDIX F: Adverse events of interest and reporting flow chart

Adverse events of interest for the trial are those relating to:

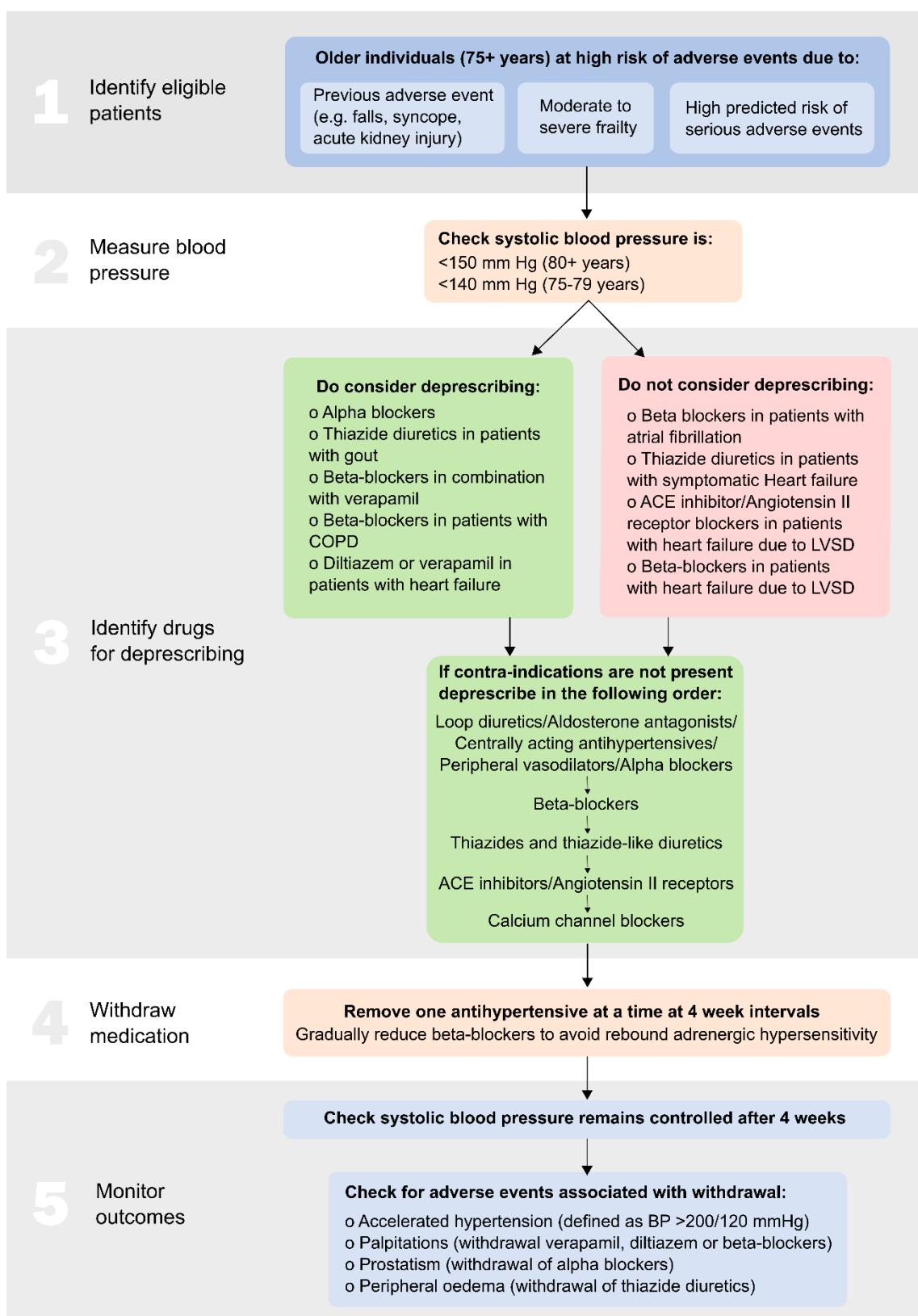
- Fractures or falls
- Circulatory system
- Kidney problems
- Electrolyte abnormalities
- Hypotension/ Syncope

All SAEs will be collected, regardless of cause.

Adverse Drug Withdrawal Events (ADWE's) will be defined in the SAP.



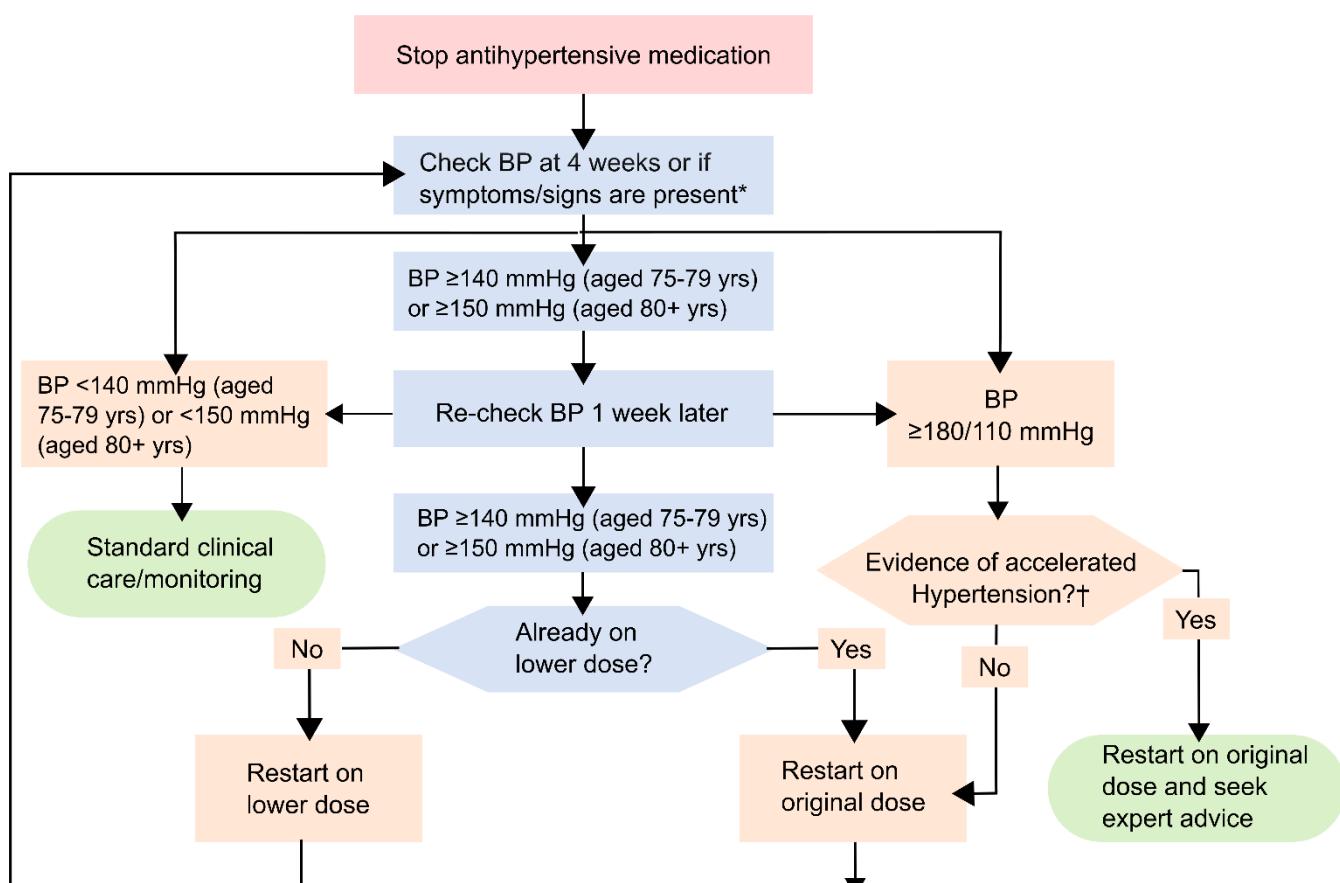
## 30. APPENDIX G: Antihypertensive deprescribing algorithm



\*Candidate drugs for deprescribing based on the STOPP/START<sup>63</sup> and STOPPFrail2<sup>64</sup> criteria, the reverse of guideline recommended treatment,<sup>22</sup> and the approach taken in the previous OPTiMISE trial.<sup>65</sup>

### 31. APPENDIX H: Post-deprescribing patient monitoring algorithm

This algorithm is for guidance. Flexibility will be allowed to ensure the participant is managed in the way deemed most appropriate by their GP (or qualified and appropriately trained health professional responsible for hypertension care or medicines management). Any additional monitoring requirements should be documented on the medication reduction plan for reference.



†For the purposes of OPTIMISE2, accelerated hypertension is defined as BP  $\geq 200/120$  mmHg, or BP  $\geq 180/110$  mmHg with additional signs or symptoms as listed below:

- Neurological symptoms: headache, seizures, confusion, cerebrovascular event
  - Respiratory symptoms: breathlessness, pulmonary oedema (and other signs of heart failure)
  - Cardiac symptoms: Chest pain
  - Vision problems: Visual disturbance, Papilloedema
  - Other symptoms: Nausea and vomiting
- Urgent (same day) expert opinion should be sought.

\*Signs and symptoms directly related to elevated BP are not anticipated, but BP should be checked if any of the following symptoms occur:

- Palpitations (withdrawal of rate-limiting drug such as verapamil, diltiazem or beta-blocker)
- Prostatism (withdrawal of alpha-blocker)
- Peripheral oedema (withdrawal of diuretic)

## 32. APPENDIX I: Amendment history

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
	1.0	30-Jan-2023	Melanie Carr	Originally submitted version
	2.0	12-Sep-2023	Melanie Carr	Version updated to 2.0 following changes during approvals process
3 (First amendment to include changes to Documents)	3.0	19-Mar-2024	Melanie Carr	<p>Addition of exclusion criterion.</p> <p>Clarification on full medication withdrawal.</p> <p>Clarification around safety visits.</p> <p>Clarification that reminders will only be sent out if response rates are low and that assessments can be undertaken by an appropriately trained researcher.</p> <p>Clarification of further antihypertensive deprescribing at safety visits, monitoring requirements on the medication reduction plan and that safety visits must be in person but can be at home.</p> <p>Correction of typos and of document used to track SAEs.</p> <p>Update that some questionnaires may be provided to the participant on paper at the baseline visit for later completion and entry by trial team.</p> <p>Update that smoking and alcohol consumption will be collected at follow-up.</p> <p>Addition of a further secondary analysis.</p>
5	4.0	27-Jun-2025	Melanie Carr	<p>Amendment of role of Dr Milensu Shanyinde.</p> <p>Changes to the protocol to update the wording around receipt of consent and reflect the move from clinical research networks to research delivery networks.</p> <p>Addition of secondary objectives and updated wording on one outcome measure from 'an' to 'at least one'.</p> <p>Change in timepoint of the ADWE endpoint from 1 year post-randomisation to 4 weeks post randomisation.</p> <p>There is no consensus in the scientific literature</p>

				as to how to define an ADWE. Following extensive consultation with the investigators it was agreed that that timing since drug withdrawal is an important factor. Events occurring within 4 weeks of withdrawal could be related to drug withdrawal, whereas, events occurring months later are less likely to be related. Therefore, in this study, we will consider those events occurring within 4 weeks as potential ADWEs and have changed the timepoint accordingly. Clarification around eligibility screening of the search report and booking procedures. Clarification around secondary analyses and removal of unnecessary details not required in the protocol, directing to the Statistical Analysis Plan for full details. Correction of Appendix C to show IPQ symptom list is also used at the 4 week safety visit, and addition to section 9.7.1 to outline this. Addition of information above Appendix H to reiterate that monitoring requirements should be outlined by the GP/Prescriber on the medication reduction plan, but that we have provided an algorithm of suggested monitoring actions.
6				No changes to protocol in this amendment
7	5.0	28-Oct-2025	Melanie Carr	Extension of planned recruitment period to reflect discussions with funder



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