Optimising Treatment for Mild Systolic Hypertension in the Elderly

STUDY PROTOCOL

V2.0 13.01.17

Trial Title: OPtimising Treatment for MIld Systolic hypertension in the Elderly: a randomised controlled trial

Internal Reference Number / Short title: OPTiMISE

Ethics Ref: 16/SC/0628

EudraCT Number: 2016-004236-38

Date and Version No: V2.0, 13.01.17

Chief Investigator:	**Professor Richard McManus** Nuffield Department of Primary Care Health Sciences University of Oxford Radcliffe Primary Care Radcliffe Observatory Quarter Woodstock Road Oxford OX2 6GG Tel: +44 (0)1865 617834 Fax: +44 (0)1865 289287 Email: richard.mcmanus@phc.ox.ac.uk
Lead Scientific Investigator:	**Dr James Sheppard** (University of Oxford)
Co-Investigators:	Prof Richard Hobbs, Prof Carl Heneghan, Dr Emma Ogburn, Dr Ly-Mee Yu, Prof Gary Ford (University of Oxford) Dr Jenni Burt, Prof Jonathan Mant, Dr John Benson **(**University of Cambridge) Dr Mark Lown, Prof Paul Little (University of Southampton) Dr Rupert Payne (University of Bristol, Bristol) Marney Williams, Lay patient advisor.
Sponsor:	University of Oxford Joint Research Office Block 60 Churchill Hospital Old Road Headington Oxford OX3 7LE

Funder: National Institute for Health Research (NIHR), Oxford Collaborations for Leadership in Applied Health Research and Care (CLARHC) and School for Primary Care Research (SPCR)

Chief Investigator Statement: I have read this protocol and agree to abide by all provisions set forth therein. I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice.

Chief Investigator Signature:

Statistician Signature:

Conflict of interest

None.

Confidentiality Statement

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

TABLE OF CONTENTS

1. KEY TRIAL CONTACTS

Chief Investigator	Professor Richard McManus **Address:** Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Primary Care, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG **Email:** richard.mcmanus@phc.ox.ac.uk **Telephone:** +44 (0)1865 617834 **Fax:** +44 (0)1865 289287
Sponsor	Ms Heather House **Address:** Clinical Trials and Research Governance, Joint Research Office, Block 60, Churchill Hospital, University of Oxford, Oxford, OX3 7LE **Email:** ctrg@admin.ox.ac.uk **Telephone:** n/a **Fax:** n/a
Clinical Trials Unit/ Statistician	Dr Ly-Mee Yu **Address:** Primary Care Clinical Trials Unit, Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Primary Care, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG **Email:** ly-mee.yu@phc.ox.ac.uk **Telephone:** +44 (0)1865 617199 **Fax:** +44 (0)1865 289287
Statistician	Dr Jill Mollison **Address:** Primary Care Clinical Trials Unit, Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Primary Care, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG **Email:** jill.mollison@phc.ox.ac.uk **Telephone:** +44 (0)1865 289300 **Fax:** +44 (0)1865 289287

2. SYNOPSIS

Trial Title	OPtimising Treatment for MIld Systolic hypertension in the Elderly: a randomised controlled trial	
Internal ref. no. (or short title)	OPTiMISE	
Clinical Phase	Phase IV trial	
Trial Design	Primary Care based, open label, randomised controlled trial with embedded qualitative components	
Trial Participants	Patients aged ≥80 years, with controlled blood pressure (systolic blood pressure <150mmHg) receiving ≥2 antihypertensive medications, with no compelling indication for medication continuation and whom the GP considers could benefit from medication reduction due to existing polypharmacy, co-morbidity and/or frailty.	
Planned Sample Size	540	
Qualitative sub-studies: participants	Interviews: 15 GPs and 15 patients potentially eligible for the trial Recording of recruitment appointments: 75 patients potentially eligible for the trial	
Treatment duration	12 weeks	
Follow up duration	12 weeks	
Planned Trial Period	01/01/2017 - 31/05/2019	
	Objectives	**Outcome Measures**
Primary	To determine if a reduction in medication can achieve a proportion of patients with clinically safe levels (defined as a systolic blood pressure <150mmHg) which is non-inferior (within 10%) to that achieved by the usual care group.	The proportion of patients with controlled systolic blood pressure levels (systolic blood pressure <150mmHg) at 12 week follow-up.
Secondary	Determine the proportion of patients in intervention arm who maintain medication reduction through to follow-up (*i.e.* are *not* restarted on therapy)	Proportion of patients randomized to the intervention arm who maintain medication reduction throughout 12 week follow-up.
	Determine the difference in quality of life (according to EQ-5D-5L) between groups at 12 week follow-up.	EQ-5D-5L score at 12 week follow-up.
	Determine the difference in frailty (according to the FRAIL scale/frailty index) between the two groups at 12 week follow-up.	FRAIL scale score/frailty index at 12 week follow-up.
	Determine the difference in the change in mean clinic systolic blood pressure (from baseline) between the two groups at 12 week follow-up.	Change in mean clinic systolic blood pressure (from baseline) at 12 week follow-up.

	Determine the difference in reported potential side effects to medication between the two groups at 12 week follow-up (e.g. coughs, dizziness, syncope, ankle swelling, etc.).	The proportion of patients reporting potential side effects to medication (e.g. coughs, dizziness, syncope, ankle swelling, etc.).
	Determine the difference in routinely reported serious adverse events between the two groups at 12 week follow-up (hospitalisation due to falls, myocardial infarction, stroke or all-cause mortality).	The proportion of patients reporting adverse events (hospitalisation due to serious falls, myocardial infarction, stroke or all-cause mortality).
	Determine the characteristics (e.g. age, gender, ethnicity, medical history) of the baseline screening and sample population and examine how these relate to individuals eligible/not eligible for recent blood pressure lowering trials conducted in the elderly.[1-3]	• Descriptive statistics of the screening and baseline population • Comparison of these characteristics with those eligible/not eligible for recent blood pressure lowering trials conducted in the elderly
Exploratory analyses	Subgroup analyses of blood pressure control, change in blood pressure and maintenance of medication reduction, by different levels of baseline frailty	The following outcomes, stratified by baseline frailty (frailty index score): • The proportion of patients with controlled systolic blood pressure levels (systolic blood pressure <150mmHg) at 12 week follow-up • Change in mean clinic systolic blood pressure (from baseline) at 12 week follow-up • Proportion of patients who maintain medication reduction throughout follow-up
	Subgroup analyses of blood pressure control, change in blood pressure and maintenance of medication reduction, by different levels of baseline functional independence	The following outcomes, stratified by baseline functional independence (modified Rankin Scale): • The proportion of patients with controlled systolic blood pressure levels (systolic blood pressure <150mmHg) at 12 week follow-up • Change in mean clinic systolic blood pressure (from baseline) at 12 week follow-up • Proportion of patients who maintain medication reduction throughout follow-up

	Subgroup analyses of blood pressure control, change in blood pressure and maintenance of medication reduction, by different levels of baseline cognitive function	The following outcomes, stratified by baseline cognitive function (MOCA score): • The proportion of patients with controlled systolic blood pressure levels (systolic blood pressure <150mmHg) at 12 week follow-up • Change in mean clinic systolic blood pressure (from baseline) at 12 week follow-up • Proportion of patients who maintain medication reduction throughout follow-up
	Subgroup analyses of blood pressure control, change in blood pressure and maintenance of medication reduction, by number of antihypertensive medications prescribed at baseline	The following outcomes, stratified by number of antihypertensive medications prescribed at baseline: • The proportion of patients with controlled systolic blood pressure levels (systolic blood pressure <150mmHg) at 12 week follow-up • Change in mean clinic systolic blood pressure (from baseline) at 12 week follow-up • Proportion of patients who maintain medication reduction throughout follow-up
	Subgroup analyses of blood pressure control, change in blood pressure and maintenance of medication reduction, by number of co-morbidities at baseline	The following outcomes, stratified by number of co-morbidities at baseline: • The proportion of patients with controlled systolic blood pressure levels (systolic blood pressure <150mmHg) at 12 week follow-up • Change in mean clinic systolic blood pressure (from baseline) at 12 week follow-up • Proportion of patients who maintain medication reduction throughout follow-up
Qualitative sub study 1: primary outcome	Determine the barriers and facilitators for patients and GPs to reducing antihypertensive medication to inform both the ongoing trial and potential future implementation.	• Thematic analysis of chart-stimulated interviews with GPs • Thematic analysis of 'Brown bag' medication review interviews with patients

Qualitative sub-study 2: primary outcome	Determine how trial recruitment is discussed and understood by recruiters and patients.	• Thematic analysis of audio-recorded recruitment appointments
Economic sub study primary outcome	Determine the cost-effectiveness of the intervention in terms of cardiovascular, quality of life and cost outcomes.	Cardiovascular disease risk, costs and quality-adjusted-life years.
Investigational Medicinal Product(s)	Medication reduction - one antihypertensive medication stopped in line with GP and patient preference and existing guidelines, where appropriate (See medication reduction algorithm in Appendix C).	
Formulation, Dose, Route of Administration	At the discretion of the consulting GP, based on indications, co-morbidities, blood pressure and guidance from the study team.	

3. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
BP	Blood pressure
CLAHRC	Collaborations for Leadership in Applied Health Research and Care
CRN	Clinical Research Network
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
CVD	Cardiovascular Disease
DMEC	Data Monitoring and Ethics Committee
eCRFs	Electronic Case Report Form
eFI	Electronic frailty index
EudraCT	European Clinical Trials Register
GCP	Good Clinical Practice
GP	General Practitioner
HYVET	HYpertension in the Very Elderly Trial
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-to-treat analysis
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial Infarction

NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NHS	National Health Service
OPTiMISE	OPtimising Treatment for MIld Systolic hypertension in the Elderly: a randomised controlled trial
PCCTU	The Oxford Primary Care and Vaccines Collaborative Clinical Trials Unit
PI	Principal Investigator
PP	Per-protocol analysis
PPI	Patient and Public Involvement
QOF	Quality and Outcomes Framework
QALY	Quality Adjusted Life Year
QoL	Quality of Life
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of medicinal Product Characteristics
SOP	Standard Operating Procedure
SPCR	School for Primary Care Research
SPRINT	Systolic blood PRessure InterventioN Trial
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

4. BACKGROUND AND RATIONALE

The population is ageing [4] and, consequently, the number of people living with age-related chronic conditions is increasing.[5] Polypharmacy is common in older persons, with up to 20% of those aged ≥80 years prescribed ten or more medications.[6] Polypharmacy is associated with increased risk of adverse drug reactions and frequent inappropriate prescribing.[7, 8] Indeed, as many as 29% of elderly people are thought to receive potentially inappropriate prescriptions in Primary Care.[9]

Hypertension is the number one co-morbid condition in older people with multiple chronic conditions [10] and 52% of those aged ≥80 years are prescribed two or more antihypertensive medications (equivalent to approximately 1.25 million people in the UK).[11] Blood pressure lowering has been shown to be effective at preventing stroke and cardiovascular disease in healthy individuals aged ≥80 years with stage 2 hypertension (systolic blood pressure of >160mmHg).[2] However, more recent evidence suggests that larger blood pressure reductions and multiple antihypertensive prescriptions may be harmful in older people.[12, 13] A meta-analysis by Bejan-Angoulvant *et al.,* found that large reductions in systolic blood pressure and higher intensity treatment may be associated with increased risk of all-cause mortality.[12] Evidence from observational studies also suggests that higher intensity blood pressure treatment is associated with increased risk of falls in older people,[14] although this is also disputed.[2]

Some patients consider the increased risk of falls and other adverse events to be as important as the risk of MI or stroke, particularly those taking medications for primary prevention of cardiovascular disease.[15] Thus, decisions over blood pressure lowering in the elderly, particularly the frail elderly, require the weighing of harms and quality of life. Studies of patients' attitudes towards hypertension treatment suggest there is widespread dislike of treatment and its side effects, fear of the long-term impact of taking medication, and consequent intentional non-adherence to treatment.[16] However, clinicians can often struggle to stop prescribing medication due to a perceived lack of evidence, fear of the reaction of other prescribers, and concern that patients will feel their care is being cut.[17, 18]

Proposed trial in the context of previous research

The recent SPRINT trial[1] showed that treatment to lower blood pressure targets (120mmHg systolic) is associated with reductions in cardiovascular morbidity and mortality. Observed reductions in total mortality were also greater in patients aged ≥75 years than in younger individuals. However, these reductions were accompanied by an increased risk of adverse events, including syncope and emergency department admission with injurious falls, although the overall rates were low. Patients enrolled in the SPRINT trial[1] were considered to be comparable to those enrolled into the HYVET study,[2, 19] and therefore less frail than general populations from Europe and North America.[20, 21] SPRINT excluded patients with diabetes, stroke, dementia and those residing in a nursing home, and thus, represent a subgroup of older individuals. Indeed, applying the SPRINT inclusion/exclusion criteria to a general population of individuals aged ≥80 years registered at general practices in the UK, reveals that one third would not have been eligible for the trial, and these individuals would have been prescribed significantly higher numbers of cardiovascular medications (increased polypharmacy) and have approximately twice the cardiovascular co-morbidity than eligible patients (table 1). The ACCORD[3] trial demonstrates that intensive blood pressure lowering may not be effective in patients with co-morbid diabetes and is

associated with significant increases in adverse events in this population. Thus, the OPTiMISE trial will specifically target those individuals with greater polypharmacy and co-morbidity.

Table 1. Characteristics of the general population aged ≥80 years who would have been eligible/not eligible for the SPRINT trial,[1] registered at 19 general practices in the West Midlands[11]

Characteristics	Not eligible for SPRINT[1] (SD or %)	Eligible for SPRINT[1] (SD or %)	Comparison of groups†	Higher in the eligible or non-eligible group?
Total population	1,350	2,291		
Demographics/risk factors				
Age (years)	85.1±4.3	85.0±4.3	0.749	Same
Sex (% female)	853 (63%)	1,497 (65%)	0.174	Same
Smoking status (% current)	84 (6%)	139 (6%)	0.851	Same
Systolic blood pressure (mmHg)*	135.5±24.1	144.5±10.3	<0.001	Eligible
Diastolic blood pressure (mmHg)*	72.5±11.2	76±9.1	<0.001	Eligible
Total cholesterol (mmol/l)*	4.4±1.1	5.0±1.1	<0.001	Eligible
HDL cholesterol (mmol/l)*	1.5±0.3	1.6±0.4	<0.001	Eligible
Prescribed treatment				
Prescribed at least 1 statin	649 (48%)	531 (23%)	<0.001	Not eligible
Prescribed at least 1 antiplatelet	676 (50%)	720 (31%)	<0.001	Not eligible
Prescribed at least 1 antihypertensive	1,061 (79%)	1,397 (61%)	<0.001	Not eligible
Prescribed at least 2 antihypertensives	766 (57%)	838 (37%)	<0.001	Not eligible
Prescribed 3 or more antihypertensives	383 (28%)	299 (13%)	<0.001	Not eligible
Co-morbidities				
Diabetes	477 (35%)	0 (0%)	<0.001	Not eligible
Chronic kidney disease	544 (40%)	576 (25%)	<0.001	Not eligible
Myocardial Infarction	149 (11%)	145 (6%)	<0.001	Not eligible
Coronary heart disease	383 (28%)	358 (16%)	<0.001	Not eligible
Stroke	210 (16%)	0 (0%)	<0.001	Not eligible
Transient ischemic attack	108 (8%)	123 (5%)	0.002	Not eligible
Heart Failure	172 (13%)	128 (6%)	<0.001	Not eligible
Peripheral vascular disease	130 (10%)	140 (6%)	<0.001	Not eligible
Total cardiovascular disease	701 (52%)	595 (26%)	<0.001	Not eligible

**Most recently recorded †Comparisons of continuous variables with independent samples t-test, comparisons of binary variables using Pearson's chi squared test; SD=standard deviation; HDL=high-density lipoprotein; Cardiovascular disease defined as myocardial infarction, coronary heart disease, stroke, transient ischemic attack, heart failure or peripheral vascular disease.*

Whilst reducing the number of antihypertensive drugs prescribed to certain older patients may be beneficial, the lack of evidence to support such an approach limits the practice in routine clinical care. We have found limited evidence from randomised trials examining the safety of antihypertensive medication reduction or withdrawal. A systematic review of medication withdrawal studies was identified which included four small trials (with between 63 and 202 participants) examining diuretic

withdrawal; this demonstrated withdrawal was maintained at follow-up in 51-81% of participants.[22] The recent DANTE study[23] examined the effect of complete antihypertensive medication discontinuation in 385 patients over the age of 75 years and with mild cognitive deficits. After 16 weeks of follow-up, they observed a 7/3mmHg increase in blood pressure but no difference in overall cognition compound score between groups (0.02 [−0.19 to 0.23]; P = 0.84) or quality of life (−0.09 [−0.34 to 0.16; P = 0.46]).

We identified one observational study,[24] which suggested that discontinuation of antihypertensive therapy may increase the risk of cardiovascular mortality in older people (>60 years), although this risk decreased overtime. The HYVET trial[2] did enrol some patients on antihypertensive treatment who were then randomised to placebo (effectively complete medication withdrawal), but there are no specific trials comparing a specified strategy of antihypertensive medication reduction with usual care in terms of effects on blood pressure control and quality of life. In addition, we have identified no previous economic modelling of a strategy of medication reduction in the elderly.

Importance of this research

The aim of this work will be to examine whether antihypertensive medication reduction in patients with controlled systolic hypertension (≤150mmHg) who are being prescribed two or more antihypertensives is possible without significant changes in blood pressure control at follow-up. This trial is needed because it is not clear what effect an intervention of medication reduction will have on blood pressure level at follow-up. Medication reduction might cause blood pressure to increase (removal of a treatment that is having a beneficial effect), which the SPRINT trial suggests may lead to adverse outcomes. In this instance, medication reduction would be deemed unsafe and treatment would be re-instated. However, the present trial will be recruiting patients who may have been taking medications for many years, potentially much longer than those enrolled into the SPRINT trial. Indeed, blood pressure may not increase with medication reduction, it might actually go down, since prescription of fewer antihypertensive therapies is associated with better adherence to medication[25] which could result in reduced blood pressure in the context of medication reduction. Alternatively, blood pressure level might not change at all, since patients may be non or partially adherent to prescribed therapy, and therefore removal of one medication may have little effect on overall blood pressure level. Indeed, just under half of individuals' prescribed antihypertensive therapy are thought to be non-adherent 12 months after the initial prescription.[26] It is these unknowns which require further investigation and provide the rationale for conducting this trial.

Older people are frequently excluded from trials [27] and our patient and public involvement suggests that some older individuals may be reluctant to participate in a clinical trial involving randomisation to new management strategies. However, previous Primary Care based studies suggest it is possible to recruit older participants to studies of cardiovascular disease prevention [2, 28] and a recent survey suggested that older individuals are willing to participate in trials for reasons of curiosity, self-interest and altruism.[29] A recent review,[30] outlined how qualitative methods may assist in ensuring robust trial procedures and interventions, including overcoming barriers to effective recruitment. The OPTiMISE trial has several potential areas of sensitivity for both patients and professionals around de-prescribing medication, and little research to date has explicitly focused on attitudes to reducing treatment in older people. Because of these areas of uncertainty, the study will have a staggered start, with two feasibility phases and concurrent qualitative work. These stages will allow aspects of trial feasibility such as recruitment to be

assessed in a small sample, before recruitment to the main trial begins. Understanding the concerns of both patients and practitioners on these issues will be crucial to the development of the study approach and materials, and to high recruitment rates.

5. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary objective To determine if a reduction in medication can achieve a proportion of patients with clinically safe levels (defined as the proportion of patients with SBP <150mmHg) which is non-inferior (within 10%) to that achieved by the usual care group.	The proportion of patients with controlled blood pressure levels at 12 week follow-up.	Baseline and 12 week follow-up.
Secondary objectives Determine the proportion of patients in intervention arm who maintain medication reduction through to follow-up (*i.e.* are *not* restarted on therapy due to unsafe increases in blood pressure)	Proportion of patients randomized to the intervention arm who maintain medication reduction throughout follow-up.	12 week follow-up.
Determine the difference in quality of life (according to EQ-5D-5L) between groups at follow-up.	EQ-5D-5L score at 12 week follow-up.	Baseline and 12 week follow-up.
Determine the difference in frailty (according to the FRAIL scale/frailty index) between the two groups at 12 week follow-up.	FRAIL scale score/frailty index at 12 week follow-up.	Baseline and 12 week follow-up.
Determine the mean difference in the change in mean clinic systolic blood pressure (from baseline) between the two groups at 12 week follow-up.	Change in mean clinic systolic blood pressure from baseline at 12 week follow-up.	Baseline and 12 week follow-up.
Determine the difference in reported potential side effects to	The proportion of patients reporting possible side effects to medication	The number of possible side effects experienced by

medication between the two groups at 12 week follow-up (e.g. coughs, dizziness, syncope, ankle swelling, etc.).	(e.g. coughs, dizziness, syncope, ankle swelling, etc.).	patients in each arm of the trial at 12 week follow-up.
Determine the difference in routinely reported adverse events between the two groups at 12 week follow-up (hospitalisation due to serious falls, myocardial infarction, stroke or all-cause mortality).	The proportion of patients reporting serious adverse events (hospitalisation due to serious falls, myocardial infarction, stroke or all-cause mortality).	The number of adverse events experienced by patients in each arm of the trial at 12 week follow-up.
Establish the characteristics of the baseline screening population, sample population and how these relate to individuals eligible/not eligible for the recent SPRINT trial.[1]	• Descriptive statistics of the screening and baseline population. • Comparison of these characteristics with those eligible/not eligible for the SPRINT trial.	Baseline only.
Exploratory analyses Subgroup analyses of blood pressure control, change in blood pressure and maintenance of medication reduction, by different levels of baseline frailty	The following outcomes, stratified by baseline frailty (frailty index score): • The proportion of patients with controlled systolic blood pressure levels (systolic blood pressure <150mmHg) at 12 week follow-up. • Change in mean clinic systolic blood pressure (from baseline) at 12 week follow-up. • Proportion of patients who maintain medication reduction throughout follow-up.	Baseline and 12 week follow-up.
Subgroup analyses of blood pressure control, change in blood pressure and maintenance of medication reduction, by different levels of baseline functional independence	The following outcomes, stratified by baseline functional independence (modified Rankin Scale): • The proportion of patients with controlled systolic blood pressure levels (systolic blood pressure <150mmHg) at 12 week follow-up. • Change in mean clinic systolic blood pressure (from baseline) at 12 week follow-up. • Proportion of patients who maintain medication reduction throughout follow-up.	Baseline and 12 week follow-up.

Subgroup analyses of blood pressure control, change in blood pressure and maintenance of medication reduction, by different levels of baseline cognitive function	The following outcomes, stratified by baseline cognitive function (MOCA score): • The proportion of patients with controlled systolic blood pressure levels (systolic blood pressure <150mmHg) at 12 week follow-up. • Change in mean clinic systolic blood pressure (from baseline) at 12 week follow-up. • Proportion of patients who maintain medication reduction throughout follow-up.	Baseline and 12 week follow-up.
Subgroup analyses of blood pressure control, change in blood pressure and maintenance of medication reduction, by number of antihypertensive medications prescribed at baseline	The following outcomes, stratified by number of antihypertensive medications prescribed at baseline: • The proportion of patients with controlled systolic blood pressure levels (systolic blood pressure <150mmHg) at 12 week follow-up. • Change in mean clinic systolic blood pressure (from baseline) at 12 week follow-up. • Proportion of patients who maintain medication reduction throughout follow-up.	Baseline and 12 week follow-up.
Subgroup analyses of blood pressure control, change in blood pressure and maintenance of medication reduction, by number of co-morbidities at baseline	The following outcomes, stratified by number of co-morbidities at baseline: • The proportion of patients with controlled systolic blood pressure levels (systolic blood pressure <150mmHg) at 12 week follow-up. • Change in mean clinic systolic blood pressure (from baseline) at 12 week follow-up. • Proportion of patients who maintain medication reduction throughout follow-up.	Baseline and 12 week follow-up.
Qualitative sub study 1 objective Determine the barriers and facilitators for patients and GPs to reducing antihypertensive medication to inform both the ongoing trial and potential future	• Thematic analysis of chart-stimulated interviews with GPs. • Thematic analysis of 'Brown bag' medication review interviews with patients.	Interviews to be carried out throughout the trial.

implementation.		
Qualitative sub-study 2 objective Determine how trial recruitment is discussed and understood by recruiters and patients.	Thematic analysis of audio-recorded recruitment appointments.	Interviews to be carried out throughout the trial.
Economic sub study objective Determine the cost-effectiveness of the intervention in terms of cardiovascular, quality of life and cost outcomes	Cardiovascular disease risk, costs and quality-adjusted-life years.	Cost-effectiveness modelling carried after final follow-up in the analysis phase of the trial.

6. TRIAL DESIGN

This trial will use a Primary Care based, open label, randomised controlled trial design. Potential participants will be invited to attend a screening visit at their GP practice and those fulfilling the eligibility criteria and giving informed consent will undergo baseline measurements for the study. Extracted data will be entered directly into the study database using eCRFs. Following baseline measurements, individuals will be randomised to a strategy of medication reduction (intervention) or usual care (control) (see Appendix A for study flow diagram). Those in the intervention arm will be invited to self-monitor their blood pressure, reporting any consistently high readings to their GP (see specific self-monitoring guidance below). All individuals in the intervention arm of the trial will be asked to attend a routine safety follow-up visit with their GP, four weeks (±2 weeks) after randomisation. All patients will attend a 12 week (±2 weeks) follow-up with the trial facilitator, either at their GP practice or at their home; the trial facilitator will repeat all measurements taken at baseline. After 12 week follow-up the trial will formally end, but passive long-term follow-up of mortality and hospital admissions will be undertaken via NHS Digital's patient tracking service.

7. PARTICIPANT IDENTIFICATION

7.1. Trial Participants

Patients eligible for the trial will be aged ≥80 years, with controlled blood pressure (systolic blood pressure <150mmHg) receiving ≥2 antihypertensive medications with no compelling indication for medication continuation and whom the GP considers may benefit from medication reduction due to existing polypharmacy, co-morbidity and frailty. A broad inclusion criteria has been chosen to make the results of this study as generalisable as possible, an important priority for all Primary Care based trials. This includes enrolling patients on long term medication for secondary prevention of cardiovascular disease who, whilst at risk of further cardiovascular events, may also be more frail and at greater risk of falls and other adverse events, and thus benefit from medication reduction. Potentially eligible patients will be identified from electronic health records using a pre-defined search strategy which can be emailed to participating practices.

7.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the trial.
- Male or Female, aged 80 years or above.
- Clinic systolic blood pressure less than 150 mmHg (according to screening measurement at baseline – clinic blood pressure defined as the mean of the 2nd and 3rd readings taken at 1 minute intervals).
- Prescribed two or more antihypertensive medications to lower blood pressure 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, potassium-sparing diuretic, alpha-blocker or beta-blocker.
- Stable dose of current antihypertensive medications for at least four weeks prior to trial entry.
- In the Investigator's opinion, could potentially benefit from medication reduction due to existing polypharmacy, co-morbidity, non-adherence or dislike of medicines and/or frailty (i.e. is different from those to which the results of the SPRINT trial are likely to apply)*
- In the Investigator's opinion, is able and willing to comply with all trial requirements.

*GPs will be given training from the research team during the site initiation visit on the findings of the SPRINT trial and other relevant trials and how these apply to patients in their practice.

7.3. Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- A participant has heart failure due to left ventricular systolic dysfunction (LVSD) and is on only ACE inhibitors/ARBs and/or beta-blockers and/or spironolactone (removing any of which would be contraindicated).
- A participant has heart failure but has not had an echocardiogram since its onset (might have undiagnosed LVSD and a compelling need for ACEI/ARB and Betablockers).
- Investigator deems that there is a compelling indication for medication continuation.
- Suffered a myocardial infarction or stroke within the past 12 months.
- Blood pressure being managed outside of primary care.
- A participant with secondary hypertension.
- A participant with previous accelerated or malignant hypertension.
- Unable to provide consent due to incapacity.
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial (e.g. terminal illness, house bound and unable to attend baseline and follow up clinics).
- Participants who have participated in another research trial involving antihypertensive medication in the past 4 weeks.

Please note, full details of inclusion and exclusion criteria for participants enrolled into the qualitative sub-studies are given in Section 10.

8. TRIAL PROCEDURES

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

8.1. Recruitment

8.1.1. Practice and GP Recruitment

All practices within the study regions (defined according to proximity with research centres) will be approached by the study team and the NIHR Clinical Research Network (CRN) with a 1-2 page Research Information Sheet for Practices (RISP) detailing the study and the GP involvement required. Our PPI engagement suggests that older patients are much more open to the idea of medication reduction if it is suggested by their own trusted GP and so full engagement from GPs will be critical to ensuring the trials' success. GPs are busy and often have little time to read through extensive study literature when considering participation in a new trial. A two minute video infographic (explaining the study rationale, which patients will be eligible and what it will involve) will also be emailed to all GPs.

8.1.2. Practice database searches

Prior to patient invitation, data will be extracted from all participating practice computer systems related to the demographics of the practice population, cardiovascular disease history, the presence of other co-morbidities, medication prescribed and overall frailty examined using the electronic frailty index (eFI).[31] Searches will be designed and conducted using the MIQUEST query tool for use in Vision practices and adapted for other practice database systems (e.g. EMISWeb) where appropriate. These data will be used to describe the general practice population, and identify who is eligible for invitation to the trial. GPs will also use these data to assess the patient's suitability to participate, including whether the patient's level of polypharmacy, co-morbidity and/or frailty means that they could potentially benefit from medication reduction. GPs will be given training by the research team at the site initiation visit regarding how to distinguish these patients from those in which recently published trials (i.e. SPRINT)[1] suggest may benefit more from medication continuation. These data will also enable the research team to examine the proportion and characteristics of individuals who would have been eligible for previous blood pressure lowering trials conducted in the elderly[1-3] and compare these to the population invited and recruited to OPTiMISE.

8.1.3. Patient Recruitment

Participants will be selected from practices across the UK. Potentially eligible patients will be identified by trained practice staff searching practice-based registers for people on two or more antihypertensive medications whose last systolic blood pressure was recorded to be <150 mmHg. Those deemed eligible will be sent letters of invitation from their GP. Patients interested in participating will be asked to return an expression of interest slip by post, email or call the study team directly using the study telephone number. Patients contacting the study team at a trial recruiting centre will be invited to attend an initial screening, recruitment and baseline clinic at their general practice (see flow chart in Appendix A). They will also be asked if they would like to receive the study video infographic via email (all potential participants will view the video infographic at the consent visit so access to email will not affect access to information about the study). Patients not responding to the first invitation will receive one reminder letter (up to four weeks after the first letter) or if possible, a direct telephone call inviting them to

participate. 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 study.

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. Those who do not wish to take part may be asked to fill in a short questionnaire detailing their reasons.

Given the age and potential lack of independence of the study population, simple, clear provision of information is likely to be important, as is engagement of carers. Indeed, evidence suggests that most patients base their informed decision on whether or not to participate in a research study on limited information.[32] Therefore, in addition to the usual patient information sheet (PIS), a simplified 2-page patient information summary sheet will be prepared summarising what will be required from participants enrolled into the study. This cover sheet will link to each section of the PIS which will provide more detail for each area. A separate, simplified information sheet for carers will also be prepared detailing the support that will be required from carers for patients choosing to participate in the study. All individuals attending a screening visit will be sent a copy of the study patient information sheet (PIS), the cover sheet, the carers information sheet and consent form so that they have chance to look at it prior to attending the clinic.

Full details of practice, GP and participant recruitment for the qualitative sub-studies are given in Section 10.

8.2. Informed Consent

Informed consent will be taken by the GP, after which the participant will move to another room for baseline screening measurements and data collection. In the invitation letter, patients will be asked if they are happy for initial study visits to be audio-recorded for qualitative analysis of recruitment appointments and data collection procedures (see section 10.2 for details). Potential participants who are happy for audio-recording of appointments will be asked to hand a signed response slip (included in the invitation letter) to the practice receptionist upon arrival for their first study visit. Consent to audio recordings will not have a bearing on an individual's care or eligibility for the main trial.

Prior the patient's appointment, participating GPs will review the patient's current antihypertensive medication regime and decide which medication 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 to be reduced, and reasons why, will be documented and pass on to the trial facilitator. The patient will not be informed of the choice of medication. During the patient appointment, the GP will show the study video infographic and go through the full PIS 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 study with the GP, and having had a chance to ask questions, those individuals willing to participate will be asked by the GP to give informed consent adhering to the relevant PC CTU Standard Operating Procedure (SOP). The patient will have read the PIS which details the study, what is required of patients, 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 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 patient, 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 wished 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. Due to the CTIMP status of this trial, individuals lacking capacity to give informed consent will excluded. The number of patients excluded for this will be monitored during the feasibility study and if it is deemed prohibitive to recruitment rates, alternative strategies will be explored with the relevant approvals for these sought via submission of a protocol amendment.

Written Informed Consent will be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The GP who obtained the consent must be suitably qualified (*i.e.* have received training in GCP) and experienced, and have been authorised to do so by the Principal Investigator. The participant or legally authorised representative must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed. A copy of the signed Informed Consent will be given to the participant. The original signed form will be sent to the PC CTU, one copy retained at site and one with the participant.

8.3. Screening and Eligibility Assessment

Those giving informed consent will then move to another room in the practice where a trained member of the research team (PCRN/research/practice staff) will complete the screening procedures which include confirmation of the patient's age, past medical history (e.g. history of stroke or heart attack in the past 12 months), current cardiovascular medication, and measurement of blood pressure.

8.4. Baseline Assessments

Remaining baseline data will be collected following confirmation of eligibility via patient questionnaires and a detailed notes review conducted by the research assistants. Variables to be collected are listed below in Appendix B. Blood pressure will be measured using the clinically validated[33] BpTRU BPM-100 blood pressure monitor which automatically records six blood pressure measurements at one minute intervals. Readings will be taken after participants have been seated for five minutes of rest and the mean of the 2nd and 3rd readings will be used the define the primary outcome. To test for orthostatic hypotension, two further readings will be taken in the standing position after one and three minutes.[34] Orthostatic hypotension will be defined as a $\geq$20mmHg drop in systolic blood pressure within three minutes of standing.

Patient characteristics and information about their medical history will be extracted from the practice records by the research assistant and entered directly into the study database. Patients will be asked to complete the following quality of life and frailty questionnaires[35-37] during their baseline and/or follow-up clinics:

- the EQ-5D 5L (Quality of life)[35]
- the self-report modified Rankin Scale (functional independence)[37]

- the FRAIL Scale[36]
- Self-report domains of the Frailty index[31, 38, 39] (see below)
- the Montreal Cognitive Assessment [MoCA])[40]
- the Medication Adherence Rating Scale (MARS) Questionnaire[41]

The frailty index is considered the most comprehensive frailty assessment[42] and can be estimated in part from a participant's medical records (in the present study it will be integrated into the electronic CRF so that certain items are not collected twice).[31] It should contain between 30-40 items of frailty (to which the answer is yes or no), but the specific number and type to include is flexible and can be adapted to a specific population or study type provided each item satisfies five simple criteria.[38, 43] The index is derived by dividing the number of frailty criteria present by the number of items assessed. The Frailty index to be used in the present study is given in Appendix C.

The 5-item FRAIL scale can be completed by the patient themselves and covers components of fatigue, resistance, ambulation, illness and weight loss. A score of 1 is attributed to each component and patients with a total score of 3-5 are classed as frail. Those with a score of 0 are considered healthy.

All questionnaire data, where possible, will be collected on a tablet computer linked to the study database. Participants will be given the option to enter responses themselves or with assistance from the research assistant. Where questionnaires are not validated for use on a tablet computer,[35] or where individuals are not comfortable using one, paper copies will be made available for completion.

8.5. Randomisation, blinding and code-breaking

Consenting patients who have completed baseline assessment will be individually randomised to one of two study arms using a web based system (Sortition®) with manual Primary Care Clinical Trials Unit (PC-CTU) back up. Participants will not be randomised until after consent has been taken and baseline assessments have been completed. Randomisation will use minimisation on practice and baseline systolic blood pressure to ensure each arm is balanced and 1:1 allocation is achieved once all participants have been recruited. The CTU programmer will test and validate the minimisation schedule to ensure the process is reproducible.

Patients randomised to the intervention will be invited to self-monitor (or have a carer monitor) their blood pressure every day for the last week of every month during the follow-up period (weeks 4, 8 and 12). Those willing to do so, will be loaned a validated blood pressure monitor for the duration of the study. We have experience of getting patients to self-monitor their blood pressure from the TASMINH-SR trial[44] and will provide the same 'traffic light system' used in that trial to identify consistently high readings requiring action by the patient (Appendix F). This action will be to schedule an appointment with their GP for further assessment of blood pressure and potential re-introduction of therapy.

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

8.6. Subsequent visits

Participants will attend one research follow-up clinic 12 weeks (±2 weeks) after baseline and those in the intervention will attend one additional safety visit at four weeks (±2 weeks). This period is expected to be sufficiently long enough to assess the impact of antihypertensive medication reduction, since these drugs

usually take approximately four weeks to 'wash out' of a patient's system. Earlier safety visits are not recommended since they could provide false reassurance that blood pressure is within safe limits if the withdrawn drug has not washed out of the participant's system.

Follow-up assessments to be conducted at each clinic are detailed in Appendix B and will include standardised blood pressure measurement (for assessment of the primary outcome), patient lifestyle characteristics, and prescribed medication. All patients attending follow-up will be asked to repeat the questionnaire assessments conducted at baseline. They will also be expected to report on their adherence to the trial medication regime and any side effect and adverse events suffered (not already documented). Follow-up appointments may be recorded (with patient consent) to permit qualitative assessment of patient experiences during the trial.

Regardless of whether individuals in the intervention arm agree to self-monitor, all those undergoing medication reduction will be asked to return to their GP for a routine safety follow-up visit approximately four weeks after randomisation. During this safety follow-up, the GP or nurse will examine the patient's blood pressure and may invite the patient for a further follow-up visit to recheck and adjust medication (dose or type) if adverse events occur or if blood pressure is sustained above 150 mmHg (Appendix E).

All patients will be flagged for mortality and hospital admissions using NHS Digital's patient tracking service, permitting long term follow-up for up to 5 years after the trial has finished.

8.7. Internal feasibility study

A trial of this type presents a number of challenges, particularly related to the recruitment of older individuals and the sensitive nature of the intervention under examination. A two stage internal feasibility study will be conducted to examine methods of patient invitation and rates of recruitment carefully, before proceeding with the main trial.

8.7.1. Feasibility phase 1

The first feasibility phase will last for a minimum of 3 months and aim to recruit approximately 25 patients from a minimum of 3-5 practices to establish whether or not anyone will be willing to participate in the study. Practices and patients will be approached for potential participation as outlined above.

8.7.2. Feasibility phase 2

The second feasibility phase of the trial will focus on recruitment rates for the main trial and whether the intended sample size is likely to be met during the recruitment period. A recruitment rate of approximately 15% of those invited is anticipated. The recruitment rate will be estimated from the those enrolled during the first feasibility phase and a further 75 patients from approximately ten practices recruited during a second phase of at least 6 months, giving an anticipated sample of 100 participants. The following actions will be considered to address varying rates of recruitment in both feasibility phases:

- If $\geq$100 patients are recruited – trial will proceed as planned

- If 75-99 patients are recruited – recruitment materials/method will be re-examined with discussions with stakeholders and patient and public involvement representatives.
- If 50-74 patients are recruited – the allocation of resources and recruitment criteria will be re-examined using information gathered from concurrent qualitative work.
- If <50 patients are recruited – the Trial Steering Committee (TSC) will decide, in discussion with the Data Monitoring and Ethics Committee (DMEC) and the funders, whether the trial should be stopped due to futility.

8.8. Discontinuation/Withdrawal of Participants from Trial Treatment

Each participant has the right to withdraw from the trial at any time. In addition, the Investigator may discontinue a participant from the trial at any time if they consider it necessary for any reason including:

- 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
- Withdrawal of Consent
- Loss to follow up

An intention-to-treat (ITT) approach will be taken so that even if medication is re-introduced to patients in the intervention group, or a patient in the control group has medication withdrawn, we will ask all participants to attend all follow-up visits as far as is practicable. 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, vital status 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.

8.9. Definition of End of Trial

The formal end of trial is the date of the last data capture following the last visit of the last participant.

9. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

9.1. Intervention group (IMP Description)

This study will use an open label design, so no blinding of the treatment allocation, or encapsulation of trial medications will be used, although treatment allocation will be concealed prior to consent and baseline assessment. Patients allocated to the intervention group of the trial will have one antihypertensive medication of the treating GP's choice stopped, in line with existing guidelines, where appropriate. Specifically, participating GPs will be encouraged to identify previously unrecognised contraindications to medication, defined by the STOPP criteria[45] (see below), and withdraw this medication:

- Thiazide diuretic with a history of gout (may exacerbate gout).

- Beta-blocker in combination with verapamil (risk of symptomatic heart block).
- Non-cardioselective beta-blocker with chronic obstructive pulmonary disease (risk of bronchospasm).
- Calcium channel blockers with chronic constipation (may exacerbate constipation).
- Use of diltiazem or verapamil with NYHA Class III or IV heart failure (may worsen heart failure).

In the absence of any obvious contraindications, or a strong clinical reason for continuing despite a STOPP criteria being met, GPs will be asked to reduce antihypertensive medications in reverse of the NICE C+A+D algorithm for older patients,[46] removing the most recently prescribed therapy beginning with thiazide (or thiazide-like) diuretics, ACE inhibitors or angiotensin II receptor blockers and then calcium channel blockers (see Appendix D). The decision to reduce antihypertensive medication will require medical input based on indications, co-morbidities and blood pressure and whilst the study team will provide the aforementioned withdrawal algorithm, the final decision will be left to the consulting GP. All patients in the trial will remain on at least one antihypertensive (the aim of the trial to assess the safety of removing one antihypertensive, not examine the optimal number/schedule of medications to reduce).

Once a medication has been removed, GPs will be expected to closely monitor the participant's response to medication reduction carefully. GPs will be given advice about what and when to monitor (Appendix E) but this will be left flexible to allow the GP to manage the patient in the way they see best. Broadly speaking, patients will be expected to return to their GP for at least one routine safety follow-up visit around 4 weeks after randomisation (±2 weeks). If systolic blood pressure increases beyond what is considered clinically safe (≥150mmHg, current target recommended by NICE)[46] during this visit, the patient will be asked to return for further safety follow-ups and if the raised blood pressure persists, or adverse events occur, GPs will be expected to re-adjust medication (dose or type), rendering the likelihood of a serious adverse event occurring very low.

All participants randomised to the medication reduction arm of the trial will be offered a blood pressure monitor for self-monitoring of blood pressure. They will be trained using protocols developed in the previous TASMIN trials[44, 47] and will be given simple and clear instructions to contact their GP if blood pressure rises above what is considered clinically safe (i.e. home systolic blood pressure >145mmHg on all readings) (see Appendix F). Patients will be asked to self-monitor (or have a carer monitor) at least 4 times per week in the last week of each month of follow-up (weeks 4, 8 and 12), although they can monitor more frequently if they wish. Differential use of self-monitoring in the intervention group, or indeed in the control group (many patients now self-monitor routinely) is not expected to impact on the study results, since there is good evidence that self-monitoring only affects blood pressure levels if used in combination with a co-intervention.[48] All other clinical care will continue as usual.

In the event that participating in this study 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.

9.2. Control group

Those allocated to the control arm of the study will continue usual clinical care (i.e. they will continue to take antihypertensive medications as prescribed and will not self-monitor unless already doing so). No other medication changes will be mandated and participating GPs will be asked to manage all other care according usual clinical practice. Individuals in the control group will not be given the option to self-monitor, although those who already self-monitor routinely (prior to the trial), or choose to begin during the trial will not be excluded.

9.3. 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). There are no validated instruments for measuring compliance with medication reduction. Nonetheless, participants will all be asked to recall if they have taken any de-prescribed medications during the follow-up period, at the 12 week visit, and their response will be documented on the CRF. Adherence to control treatments and remaining therapies (which have not been de-prescribed) will be examined at follow-up by giving each patient the Medication Adherence Rating Scale (MARS) Questionnaire.[41] GP prescribing data will be collected from practice computer systems by the research assistant as a measure of GP compliance with the study protocol.

9.4. Concomitant Medication

All other (non-blood pressure lowering) medication taken by participants will be at the discretion of participating practices. No other medication changes will be mandated and participating GPs will be asked to manage all other care according usual clinical practice. Prescribed and relevant over the counter medications taken will be recorded at baseline and follow-up.

9.5. Post-trial Treatment

Continuation of medication reduction after the trial is complete will be at the discretion of the consulting GP. The patient remains the responsibility of their GP during and after the trial, and therefore under will continue under normal care. The study team will not provide further guidance on medication reduction, or provide blood pressure monitors for self-monitoring of blood pressure outside the trial period.

10. QUALITATIVE SUB STUDIES

Embedded within the trial will be two qualitative studies: scoping work to understand the perspectives of patients and GPs and to inform recruitment approaches, followed by an iterative examination of recruitment within the trial. This work will be led and coordinated from Cambridge.

10.1. Qualitative study 1: interviews with doctors and patient

To generate understanding about the barriers and facilitators to reducing antihypertensive medications, and inform development of trial recruitment procedures and materials, we will conduct face-to-face interviews with GPs and patients. These will take place prior to the main trial.

10.1.1. Participant identification and recruitment

Both GPs and patients will be recruited to participate in the first interview study from practices within the Cambridgeshire study region. The study team will, in discussion with the NIHR Clinical Research Network (CRN), approach potential GP participants with an information sheet outlining what participation would involve. All interested GPs will be followed up by a member of the study team to discuss the interview and the requirements of the chart-stimulated recall approach (see below for details of this). In line with qualitative sampling approaches, we will seek a broad range of opinion by endeavouring to approach GPs working in varying practice settings, including larger and smaller practise sizes and both rural and urban locations. We anticipate interviewing around 15 GPs in total: analysis will commence alongside subsequent interviews to enable the study team to monitor the depth and range of data being collected.

GPs agreeing to participate in an interview will be asked, in collaboration with practice staff, to identify potential patients to additionally approach for interview. We will apply the same inclusion criteria as in the trial, seeking to interview patients aged $\geq$80 years, with controlled blood pressure (systolic blood pressure <150mmHg) receiving ≥2 antihypertensive medications with no compelling indication for medication continuation and whom the GP considers may benefit from medication reduction due to existing polypharmacy, co-morbidity and frailty. However, in contrast with the trial, the only exclusion criteria at interview will be capacity to consent to and participate in an interview, as determined by the GP. Those deemed eligible will be sent letters of invitation from their GP, including a participant information sheet and consent form. Patients will also be approached opportunistically, via a telephone call from their GP, or, in those participants enrolled into the main trial who agree, via a telephone call from the research team. Those expressing an interest in the study over the phone will be sent a participant information sheet and consent form.

Patients interested in participating will be asked to return an expression of interest slip by post, email or call the study team directly using the study telephone number: a researcher will then arrange a convenient time for interview. Patients not responding to the first invitation will receive one reminder letter (up to four weeks after the first letter) or if possible, a direct telephone call inviting them to participate. 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 study.

Interviews will take place at a convenient location for the patient, such as in their own home or, if they prefer, at their GP practice. As with GPs, we anticipate conducting around 15 interviews with patients to generate sufficient data for the purposes of our analyses.

10.1.2. Informed consent

For both GPs and patients, written informed consent will be taken by the researcher prior to the commencement of each interview. If participants have previously sent a consent form to the study team prior to the date on which the interview takes place, this will be reviewed and verbally re-confirmed. Consent forms will include permission to audio-record the interview and for anonymised quotes to be used in research reports and publications.

10.1.3. Interview approach

Interviews with GPs will use a chart-stimulated recall approach to explore the factors, which influence their treatment choices in older hypertensive patients. We will draw on anonymised records from patients eligible for the main trial, using these to focus discussions about how GPs would feel about reducing antihypertensive medications in these patients. To achieve this, participating GPs will be asked, prior to the interview, to identify two patients whose clinical cases they would like to reflect on. Patient anonymity will be protected at all times: GPs will be asked not to divulge patient-identifiable information during interviews, such as names or residential locations. During the interview, discussions will include how a medication reduction decision might vary between patients, and include open-ended questions focusing on the doctor's approach to the management of hypertension and how this has changed over time.

Interviews with patients will use 'brown bag' medication review techniques[49] to work together during the interview to create a complete record of medication held, with a commentary on usage from the participants' perspective. Following this logging exercise, we will use diagrammatic elicitation techniques in which interviewees are supported to complete a relational map outlining their conditions and medications and their perceived inter-relationships and meaning. These sketches will be used as the basis for a discussion on the implications of withdrawing antihypertensive medications, and what this "gap" might mean for the patient. Open-ended questions will focus on perceptions of their need for and role of antihypertensives, experiences of being on antihypertensives, and perceived needs after cessation of treatment.

10.1.4. Data analysis

All interviews will be transcribed verbatim. Visual data will be digitally scanned. All data will be stored and organised in NVivo. Interview and visual data from GP and patient interviews will be subjected to thematic analysis, with a particular orientation to exploring clinical and patient perspectives on the barriers and facilitators to reducing anti-hypertensives. Analyses will be used both inform the development of materials and approaches to be used in the trial and to understand GPs' and patients' attitudes to and concerns regarding medication burden and optimisation.

10.2. Qualitative study 2: assessment of trial recruitment and data collection procedures

The aim of this second qualitative study will be to inform understanding of the presentation of information within recruitment appointments, and how this might impact on consent to participate, with a view to ensuring robust procedures in an iterative process. We will draw on methods previously used in the ProtecT trial,[50] and further developed by the QuinteT (Qualitative Research Integrated in Trials)[51] team, aiming to facilitate the ability of patients to make an informed decision about their participation in the trial. To achieve this, we will audio record consultations between GPs/research assistants and eligible patients, to observe the nature of discussions about the OPTiMISE trial. This qualitative study is fully embedded within the conduct of the feasibility trial: full consent procedures are outlined in section 8.2. We will aim to record about 15 consultations at each of five practices in the internal feasibility study, giving us a pool of 75 consultations for analysis. Assuming recruitment rates of around 15% are achieved, approximately 10 -12 observed consultations would include a patient who consents to participate. We will also record a subset of follow-up appointments to examine patient's experiences of participating in the trial.

Thematic analysis will be undertaken on a sample of around 15-20 consultations comprising patients who did/did not consent to participate, to consider (a) terminology used, (b) presentation of the deprescribing approach and (c) presentation of randomisation. This will inform on-going trial procedures and future implementation should the results suggest that medication reduction is an appropriate strategy in older individuals.

10.3. Integration of qualitative sub-studies with trial procedures

To ensure swift implementation of procedural changes as a result of themes identified through concurrent data analysis in the qualitative studies, we will hold two dissemination 'away days' with the study team. These days will be designed specifically to debate observations and analytical ideas identified through the qualitative interviews alongside the latest recruitment rates from the feasibility study, and to subsequently plan strategies to deal with any arising issues. They will offer a longer, more focused time to develop strategies which will maximise the success of the trial, compared to traditional trial steering committees. Monthly meetings across centres, and bi-annual steering committee meetings will also be held to ensure appropriate flow of information between all members of the multi-centre project team.

11. ECONOMIC SUB STUDY

We have previously developed Markov cost-effectiveness models to estimate the long-term costs and benefits from blood pressure lowering in younger populations.[52] These models do not include harms of treatment, which are assumed similar in both arms, an assumption which may not hold in an older population. We will adapt this model to include harms of treatment with adjustment of the effects of blood pressure lowering on cardiovascular disease risk, costs and quality-adjusted-life years (QALYs) to match the older population involved in this work. Particular attention will be given to how small changes in blood pressure level impact on patient outcomes, regardless of whether or not the trial demonstrates medication reduction to be non-inferior to usual care. Costs of the therapies prescribed, side effects and acute and long term costs of cardiovascular events will be obtained within the trial and from the literature. Quality of life on each treatment strategy will be obtained from the trial data on EQ-5D 5L, and previous studies will inform utility values for cardiovascular disease health states impact of side effects. The model will determine the cost per additional QALY gained of the medication reduction intervention versus usual care and analysis will be from a health and social services perspective. The model will be run over patient lifetime, with costs and benefits discounted at a rate of 3.5%. Extensive sensitivity analyses, including probabilistic sensitivity analysis, will evaluate parameter uncertainty and a value of information exercise will assess whether a further trial would be appropriate and which parameters would be most sensitive to change and should therefore be chosen as outcomes for such a trial. This work will be led by S Jowett (Honorary Senior Lecturer at Keele University).

12. SAFETY REPORTING

12.1. Definitions

Adverse Event (AE)	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.

Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose which is/or is not administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication (or lack of) and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consist of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. 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.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one (or lack of) of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction deemed by the investigator to be either related to the medication withdrawal (the study IMP) or the nature and severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC) for that product.

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. 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
- **Possibly** – although a relationship to the IMP 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.
- **Definitely** – the known effects of the IMP, its therapeutics class or based on challenge testing suggest that the IMP is the most likely cause.

All AEs (SAEs) labelled possibly, probably or definitely will be considered as related to the IMP.

12.3. Trial specific issues around patient safety

This trial has important safety issues which are described and addressed below.

12.3.1. Risks of treatment/medication reduction

In this elderly, potentially frail population, the major risks of treatment are the potential for falls due to lower blood pressure which can lead to subsequent complications and sometimes death. Medication reduction could be associated with an increased risk of major cardiovascular events or cardiac failure. All patients enrolled into the trial will be informed of the risks of medication continuation and/or reduction in patient information sheets prior to consent and will be followed up carefully throughout the trial.

12.3.2. Trial follow-up

Potential 'side effects' to medication reduction will be monitored with self-monitoring of blood pressure and by the consulting GP or practice nurse at the scheduled 4 week follow-up. This period of follow-up was chosen because it will ensure complete drug washout (most treatment trials wait at least month between instructing patients to stop taking medication and measuring blood pressure in the trial run-in phase) and is in keeping with standard procedures when adding/removing drugs in routine practice. The trial is sufficiently short that if any serious adverse events were to occur in one of the trial arms (e.g. MI or stroke), the trial could be stopped before significant numbers of individuals came to harm.

12.3.3. Measures to minimise the risks associated with medication reduction

To ensure the risks to patients enrolled in the intervention arm of the trial are not unacceptably high, strict criteria for re-introducing medications will be mandated and the consulting GP's application of these criteria throughout the trial will be monitored by the data monitoring committee. Specifically, GPs will be expected to re-introduce therapy if the patient presents with one of the following:

a) The patient has a clinic systolic blood pressure reading >150 mmHg (defined as the mean of 2nd and 3rd readings taken within the same visit) following 3 consecutive days of systolic home blood pressure readings above 145 mmHg, taken within one week.

b) The patient has a clinic systolic blood pressure reading >150 mmHg (defined as the mean of 2nd and 3rd readings taken within the same visit) at repeated safety follow-up visits.
c) The GP feels there is a clinical need for re-introduction of treatment

12.4. Recording Procedures for Adverse Events

All site staff will be appropriately trained in the procedures to follow and the forms to use by the PC-CTU prior to study initiation. Regular central monitoring for all studies and site monitoring, as determined by the trial specific risk assessment, will be used to ensure that all adverse events are identified and acted on appropriately.

Adverse events that are observed by the Investigator or reported by the participant may be reported at any time but will be specifically asked about and recorded on the CRF at 12 week follow-up, whether or not attributed to trial intervention.

The following information will be recorded: 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.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe. The severity of events, and the relationship of AEs to the study medication, will be assessed by the local medically qualified investigator or a medically qualified member of the research team. AEs considered related to the withdrawal of medication (the intervention), will be followed until resolution or the event is considered stable, clinically insignificant or asymptomatic. All related AEs that result in a participant's withdrawal from the study or are present at the end of the study, 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.

12.5. Reporting Procedures for Serious Adverse Events

All SAEs occurring during the study (from randomisation to the end of the individual's 12 week follow-up appointment), either observed by the recruiting physician or reported by the participant, whether or not attributed to study 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 faxed and/or 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:

- Description
- Date of onset
- End date
- Severity
- Assessment of relatedness to study medication

- Other suspect drug or device
- Action taken

Follow-up information should be provided as necessary.

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 and faxed 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 or fax and telephone ahead.

The documentation will be reviewed by the Trial Management Team and the 'SAE Checklist' will be completed and retained by the PC-CTU. Following the initial check of the report, any additional information will be requested, and the CI 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 SAE reports are reviewed by the DMEC, at meetings held every 6 months. 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 paper SAE Report Form (i.e. updating the original form) and returned to the PC-CTU by email or fax 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 complete regular reports 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 study. Any concerns identified will be immediately raised with the Chief Investigator and may be tabled for discussion at the regular PC-CTU Management Committee meetings or referred to the study's DMEC for review. The DMEC also monitors the frequency and pattern of events reported as part of its independent oversight of the trial. The expectedness of adverse events occurring as a result of re-introduction of withdrawn medication will be determined according to the latest version of the Summary of medicinal Product Characteristics (SmPC, section 4.8). There are no sections of the SmPC, or previous clinical studies which detail expected adverse events as a result of medication withdrawal (the study IMP) and therefore all SAEs at least possibly related, and not as a result of re-introduction of withdrawn medication, will be considered unexpected and reported as SUSARs.

12.6. Reporting Procedures for SUSAR

All SUSARs will be reported by the CI 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. Treatment codes will be un-blinded for specific participants.

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. Data Monitoring and Ethics Committee

A DMEC will be convened, including a GP/Geriatrician, statistician and consultant clinical pharmacologist. They will convene regularly prior to, during and following the trial, and will report to and advise the TSC and the TMG. The TSC will have independent chairs and 'stop guideline' authority to advise early termination of the trial in the event of safety concerns or futility such as poor recruitment rates. Together, 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.

12.8. Development Safety Update Reports

In addition to the expedited reporting above, the CI shall submit a Developmental Safety Update Report to the Competent Authority (the MHRA), Ethics Committee, Host NHS Trust and sponsor in line with PC-CTU SOP TM119 "Pharmacovigilance". This report will be submitted once a year throughout the trial within 60 days of the date of the anniversary of the CTA, or on request.

13. STATISTICS

A Statistical Analysis Plan for all analyses to be conducted will be produced separately. Below is a brief summary of the main proposed analyses. Qualitative and cost-effectiveness analyses are described in sections 10 and 11 respectively.

13.1. Description of Statistical Methods

The primary and secondary analyses will be by ITT, unless explicitly stated otherwise. The primary analysis will be a non-inferiority analysis by means of the "two one-sided test" (TOST) procedure,[53] whereby the $(1 - 2\alpha) \times 100\%$ confidence interval for the relative risk of participants with systolic blood pressure at 12 weeks below 150mmHg between the medication reduction group and the usual care group is calculated. Therefore, for $\alpha = 0.025$ the 95% confidence interval will be calculated. If the lower limit of the confidence interval is more than 0.9 (equal to a risk difference of 10%) then the research

hypothesis that medication reduction will by non-inferior in terms of blood pressure control to usual care will be accepted.

The relative risk and its confidence interval will be obtained by means of a generalised linear mixed effects model specifying a binomial distribution with a log link function. The response will be binary indicator of whether the person has a systolic blood pressure below 150mmHg at 12 weeks. Practice will be included in the model as a random effect. Adjustment will be made for baseline blood pressure by including it as a fixed effect. In addition, covariates found to be predictive of missingness will be included in the model.

As a secondary analysis of the primary outcome, a per-protocol (PP) analysis will be performed. The purpose of this analysis to support the non-inferiority research hypothesis, as an ITT analysis can be anticonservative for a non-inferiority hypothesis.[53] Participants who received the medication reduction intervention in the PP analysis will be defined as a participant in the medication reduction arm who maintained their medication reduction throughout the 12 week follow-up period. Accepting the research hypothesis for both ITT and PP analyses will lend strength to the conclusions of the study. If the PP analysis leads to a different conclusion, then the reasons for non-compliance of participants who did not follow the medication reduction intervention will be investigated to explain the discrepancy. To support this investigation, as a secondary analysis the proportion of participants in the medication reduction arm who maintained their medication reduction throughout the 12 week follow-up period will be reported.

The difference between the intervention and usual care of the changes in the following secondary outcomes will be analysed by means of linear mixed effects model, adjusting for the baseline level of the outcome and baseline systolic blood pressure and including practice as a random effect: systolic blood pressure, EQ-5D-5L and the Frailty index/frail scale. The difference in the rate of side effects and adverse events between the medication reduction and usual care arms will be analysed by means of a logistic mixed effects model adjusting for baseline systolic blood pressure and including practice as a random effect.

Exploratory subgroup analyses of blood pressure control, change in blood pressure and maintenance of medication reduction will be conducted by different levels of baseline frailty, functional independence, cognitive function, number of medications prescribed at baseline and number of co-morbidities at baseline.

A sensitivity analysis will be conducted where participants whose BP was measured at home will be excluded from the analysis, as well as an analysis where the BP measurements are imputed for these participants. The results of these two sensitivity analyses will be compared to the primary analysis to examine whether the place of measurement affects the primary outcome.

13.2. The Number of Participants

Assuming that 100% of patients in the usual care group, and 96% of those in the medication reduction group have controlled systolic blood pressure levels (<150mmHg) at follow-up, approximately 540 patients would be required to detect a non-inferior difference in systolic blood pressure control between groups. Calculations assume a 10% non-inferiority margin, 90% power, alpha of 2.5%, 10% loss to follow-up and a 10% dilution effect due to cross-over between arms. There is no existing precedent for an appropriate margin of non-inferiority in a trial of this nature and the paucity of existing literature on the

topic makes one difficult to model. The margin of 10% has been chosen to inform future doctor-patient discussions about medication reduction: if the non-inferiority margin is met, it will suggest that for every ten patients who have their medication reduced, nine will still have controlled blood pressure at 12 weeks follow-up.

Based on previous data from Primary Care,[11] approximately 92 patients would be eligible for this study per practice recruited (average sized [n=7,000]). Assuming a conservative recruitment rate of 15%, we would require approximately 39 practices (13 from each of three centres: Oxford, Cambridge, Southampton), each randomising 14 patients to the study.

13.3. The Level of Statistical Significance

For the non-inferiority analysis, the two one sided test procedure will be used with the level of significance set at 2.5%. For all other analyses, the level of significance will be 5% two-sided significant level. P-values will be adjusted for any multiple comparisons in order to maintain an overall type I error rate of 5%.

13.4. Criteria for the Termination of the Trial

The trial is of a method of management through medication reduction, rather than a specific medicinal product. It is not anticipated that the trial will be terminated unless on the advice of the DMEC in the case of a series of Suspected Unexpected Serious Adverse Reactions (SUSARs). No statistical interim analysis is planned for the main trial.

13.5. 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.

13.6. Inclusion in Analysis

All data will be included in the analysis as far as possible to allow full ITT analysis, though there will inevitably be the problem of missing data due to withdrawal, loss to follow-up, or non-response questionnaire items. For the PP analysis, all participants will be included in the analysis, but those participants randomised to the medication reduction arm will be assigned to the control arm if they failed to maintain their medication reduction throughout the 12 week follow-up period.

13.7. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

The final statistical 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

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, diaries, 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.

14.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution (University of Oxford OPTiMISE research team) and the regulatory authorities to permit trial-related monitoring, audits and inspections. To ensure data transparency, the trial has been registered on the EU Clinical Trials Register (EudraCT) and will be registered on the International Standard Randomised Controlled Trial Number (ISRCTN) registry before the first participant is recruited.

14.3. Data Handling and Record Keeping

All trial data (expect specific questionnaires not validated for electronic data capture) will be entered on to electronic CRFs which will link directly to the trial database. This 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 study ID to offer patient confidentiality and protect against bias. A separate database 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. The identifiers will be held separately from the CRFs collecting clinical data. The unique study identifier will generated for every patient enrolled to the study and this will be entered onto both study databases to permit linkage of identifiable and anonymised clinical data where necessary. Double data entry will be employed for entry of the unique study identifier onto both databases to ensure accuracy. 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 study supervised by Oxford PC-CTU's Senior Clinical Data Specialist and PC-CTU SOPs will be followed.

15. QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and PC-CTU standard operating procedures. The PC-CTU has in place procedures for assessing risk management for trials which will outline the monitoring required. The investigators and all trial related site staff will receive appropriate training in Good Clinical Practice and trial procedures.

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 PC-CTU 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 manager, statistician, data manager) and will meet regularly throughout the course of the trial.

A 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 role of a TSC is to provide overall supervision of the trial and ensure that it is being conducted 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 consist of members who are independent of the investigators, in particular an independent chairperson.

An independent DMEC meet at 6 monthly intervals before, and until the end of the trial. 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 (See section 12.6).

16. SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations, PC-CTU SOP TM125 "Trial Related Deviations and Serious Breaches" contains 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".

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the NHS host organisation within seven calendar days.

17. ETHICAL AND REGULATORY CONSIDERATIONS

17.1. Declaration of Helsinki

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

17.2. Guidelines for Good Clinical Practice

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

17.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), host institution(s) and HRA for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

17.4. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, host organisation and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

17.5. Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all trial documents and in the electronic clinical database. All data will be stored securely on an electronic study database in line with the Data Protection Act 1998 and NHS policy. The study database will be managed according to Standard Operating Procedures maintained by the PC CTU. Access rights to data and applications software will be clearly defined and staff authorised to access personal data will be formally notified in writing of the permissible scope of their access. Data access will be limited to specific members of the research team (trained in data protection policy) including the chief investigator (as study guarantor), data manager and database programmer. For each database application, system users will be given a valid user system account name (username ID), and a password known only to that user to prevent unauthorised use of systems. All data will be entered into the database through a reliably encrypted gateway.

Confidentiality of potential participants in the programme will be maintained by making the initial searches of the practice computer systems and subsequent study invitations the responsibility of the practice. All data held in paper form (e.g. consent forms) will be kept in locked filing cabinets and will only be accessible by trial staff and authorised personnel.

17.6. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate. For patients with limited mobility and no access to their own form of transport, pre-paid taxis will be offered to ensure that accessibility doesn't prevent them from being able to participate. Patients in the intervention arm of the study will be provided with clinically validated BP monitoring equipment during the trial.

17.7. Other Ethical Considerations

This research involves older participants, some of whom may be considered vulnerable. This is necessary since it is these frail, vulnerable populations who could potentially gain the most from antihypertensive medication reduction. Great care will be taken to ensure all potential participants have the trial clearly explained, and are given sufficient time to decide whether to give informed consent. This will include provision of simplified, patient information sheets with large fonts, video infographics to explain the study to those who find it difficult to read and extended GP consultation periods for explaining the study and taking informed consent.

We do not anticipate any other ethical considerations, other than those outlined above.

18. FINANCE AND INSURANCE

18.1. Funding

This trial is funded by the National Institute for Health Research (NIHR) Oxford Collaborations for Leadership in Applied Research and Care (CLARHC) and the NIHR School for Primary Care Research (SPCR).

18.2. Insurance

The University 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 that is provided.

19. PUBLICATION POLICY

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

All research outputs from this work will be published in peer-reviewed journals. Study findings will be presented at regional, national and international conferences to ensure maximum dissemination amongst academic and clinical colleagues. Where possible, local and national media will be engaged to bring the research findings to a wider audience. We will also use social media (e.g. Twitter, blogs) to disseminate the progress and findings to a wider audience. 'Patient friendly' study summary documents and infographics will be made available to all participants at the end of the trial via the study website and distributed to relevant patient groups (e.g British Heart Foundation, Age UK), ensuring widespread dissemination amongst service users. Regular trial updates and final results will be further disseminated using the communication structures developed by the NIHR Oxford CLAHRC and the SPCR (website, newsletters, symposia, etc.).

It is anticipated that the findings of this trial will support better patient-centred management plans for the prevention of cardiovascular disease in older individuals and will be made available for the next iterations of the NICE hypertension and multi-morbidity guidelines.

20. REFERENCES

1. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *The New England journal of medicine* 2015.

2. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ. Treatment of hypertension in patients 80 years of age or older. *The New England journal of medicine* 2008; **358**(18): 1887-98.

3. Cushman WC, Evans GW, Byington RP, Goff DC, Jr., Grimm RH, Jr., Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *The New England journal of medicine* 2010; **362**(17): 1575-85.

4. Office for National Statistics. http://www.ons.gov.uk, 2010.

5. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012; **380**(9836): 37-43.

6. Payne RA, Avery AJ, Duerden M, Saunders CL, Simpson CR, Abel GA. Prevalence of polypharmacy in a Scottish primary care population. *European journal of clinical pharmacology* 2014; **70**(5): 575-81.

7. Bradley MC, Motterlini N, Padmanabhan S, Cahir C, Williams T, Fahey T, Hughes CM. Potentially inappropriate prescribing among older people in the United Kingdom. *BMC geriatrics* 2014; **14**: 72.

8. Sato I, Akazawa M. Polypharmacy and adverse drug reactions in Japanese elderly taking antihypertensives: a retrospective database study. *Drug, healthcare and patient safety* 2013; **5**: 143-50.

9. Opondo D, Eslami S, Visscher S, de Rooij SE, Verheij R, Korevaar JC, Abu-Hanna A. Inappropriateness of medication prescriptions to elderly patients in the primary care setting: a systematic review. *PloS one* 2012; **7**(8): e43617.

10. Violan C, Foguet-Boreu Q, Roso-Llorach A, Rodriguez-Blanco T, Pons-Vigues M, Pujol-Ribera E, Munoz-Perez MA, Valderas JM. Burden of multimorbidity, socioeconomic status and use of health services across stages of life in urban areas: a cross-sectional study. *BMC public health* 2014; **14**: 530.

11. Sheppard JP, Singh S, Fletcher K, McManus RJ, Mant J. Impact of age and sex on primary preventive treatment for cardiovascular disease in the West Midlands, UK: cross sectional study. *BMJ (Clinical research ed)* 2012; **345**: e4535.

12. Bejan-Angoulvant T, Saadatian-Elahi M, Wright JM, Schron EB, Lindholm LH, Fagard R, Staessen JA, Gueyffier F. Treatment of hypertension in patients 80 years and older: the lower the better? A meta-analysis of randomized controlled trials. *Journal of hypertension* 2010; **28**(7): 1366-72.

13. Benetos A, Labat C, Rossignol P, Fay R, Rolland Y, Valbusa F, Salvi P, Zamboni M, Manckoundia P, Hanon O, Gautier S. Treatment With Multiple Blood Pressure Medications, Achieved Blood

Pressure, and Mortality in Older Nursing Home Residents: The PARTAGE Study. *JAMA internal medicine* 2015.

14. Tinetti ME, Han L, Lee DS, McAvay GJ, Peduzzi P, Gross CP, Zhou B, Lin H. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. *JAMA internal medicine* 2014; **174**(4): 588-95.

15. Fried TR, Tinetti ME, Towle V, O'Leary JR, Iannone L. Effects of benefits and harms on older persons' willingness to take medication for primary cardiovascular prevention. *Archives of internal medicine* 2011; **171**(10): 923-8.

16. Marshall IJ, Wolfe CD, McKevitt C. Lay perspectives on hypertension and drug adherence: systematic review of qualitative research. *BMJ (Clinical research ed)* 2012; **345**: e3953.

17. Schuling J, Gebben H, Veehof LJ, Haaijer-Ruskamp FM. Deprescribing medication in very elderly patients with multimorbidity: the view of Dutch GPs. A qualitative study. *BMC family practice* 2012; **13**: 56.

18. Scott IA, Anderson K, Freeman CR, Stowasser DA. First do no harm: a real need to deprescribe in older patients. *The Medical journal of Australia* 2014; **201**(7): 390-2.

19. Pajewski NM, Williamson JD, Applegate WB, Berlowitz DR, Bolin LP, Chertow GM, Krousel-Wood MA, Lopez-Barrera N, Powell JR, Roumie CL, Still C, Sink KM, Tang R, Wright CB, Supiano MA. Characterizing Frailty Status in the Systolic Blood Pressure Intervention Trial. *The journals of gerontology Series A, Biological sciences and medical sciences* 2016; **71**(5): 649-55.

20. Kulminski A, Yashin A, Ukraintseva S, Akushevich I, Arbeev K, Land K, Manton K. Accumulation of health disorders as a systemic measure of aging: Findings from the NLTCS data. *Mechanisms of ageing and development* 2006; **127**(11): 840-8.

21. Romero-Ortuno R, Kenny RA. The frailty index in Europeans: association with age and mortality. *Age and ageing* 2012; **41**(5): 684-9.

22. Iyer S, Naganathan V, McLachlan AJ, Le Couteur DG. Medication withdrawal trials in people aged 65 years and older: a systematic review. *Drugs & aging* 2008; **25**(12): 1021-31.

23. Moonen JE, Foster-Dingley JC, de Ruijter W, van der Grond J, Bertens AS, van Buchem MA, Gussekloo J, Middelkoop HA, Wermer MJ, Westendorp RG, de Craen AJ, van der Mast RC. Effect of Discontinuation of Antihypertensive Treatment in Elderly People on Cognitive Functioning--the DANTE Study Leiden: A Randomized Clinical Trial. *JAMA internal medicine* 2015; **175**(10): 1622-30.

24. Correa Leite ML, Firmo JO, Loyola Filho AI, Lima-Costa MF. Discontinuation of anti-hypertensive drugs increases 11-year cardiovascular mortality risk in community-dwelling elderly (the Bambui Cohort Study of Ageing). *BMC public health* 2014; **14**: 725.

25. Chapman RH, Benner JS, Petrilla AA, Tierce JC, Collins SR, Battleman DS, Schwartz JS. Predictors of adherence with antihypertensive and lipid-lowering therapy. *Archives of internal medicine* 2005; **165**(10): 1147-52.

26. Chapman RH, Petrilla AA, Benner JS, Schwartz JS, Tang SS. Predictors of adherence to concomitant antihypertensive and lipid-lowering medications in older adults: a retrospective, cohort study. *Drugs & aging* 2008; **25**(10): 885-92.

27. Califf RM, Alexander KP. Cardiovascular research in the elderly: challenges, opportunities, and impact. *Postgraduate medicine* 2002; **112**(6 Suppl Heart): 6-11.

28. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007; **370**(9586): 493-503.

29. Tolmie EP, Mungall MM, Louden G, Lindsay GM, Gaw A. Understanding why older people participate in clinical trials: the experience of the Scottish PROSPER participants. *Age and ageing* 2004; **33**(4): 374-8.

30. Fletcher B, Gheorghe A, Moore D, Wilson S, Damery S. Improving the recruitment activity of clinicians in randomised controlled trials: a systematic review. *BMJ open* 2012; **2**(1): e000496.

31. Clegg A, Bates C, Young J, Ryan R, Nichols L, Ann Teale E, Mohammed MA, Parry J, Marshall T. Development and validation of an electronic frailty index using routine primary care electronic health record data. *Age and ageing* 2016; **45**(3): 353-60.

32. Antoniou EE, Draper H, Reed K, Burls A, Southwood TR, Zeegers MP. An empirical study on the preferred size of the participant information sheet in research. *Journal of medical ethics* 2011; **37**(9): 557-62.

33. Mattu GS, Heran BS, Wright JM. Overall accuracy of the BpTRU--an automated electronic blood pressure device. *Blood pressure monitoring* 2004; **9**(1): 47-52.

34. Lahrmann H, Cortelli P, Hilz M, Mathias CJ, Struhal W, Tassinari M. EFNS guidelines on the diagnosis and management of orthostatic hypotension. *European journal of neurology* 2006; **13**(9): 930-6.

35. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* 2011; **20**(10): 1727-36.

36. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *The journal of nutrition, health & aging* 2012; **16**(7): 601-8.

37. Sulter G, Steen C, De Keyser J. Use of the Barthel index and modified Rankin scale in acute stroke trials. *Stroke; a journal of cerebral circulation* 1999; **30**(8): 1538-41.

38. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *TheScientificWorldJournal* 2001; **1**: 323-36.

39. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A. A global clinical measure of fitness and frailty in elderly people. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 2005; **173**(5): 489-95.

40. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society* 2005; **53**(4): 695-9.

41. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *Journal of psychosomatic research* 1999; **47**(6): 555-67.

42. de Vries NM, Staal JB, van Ravensberg CD, Hobbelen JS, Olde Rikkert MG, Nijhuis-van der Sanden MW. Outcome instruments to measure frailty: a systematic review. *Ageing research reviews* 2011; **10**(1): 104-14.

43. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC geriatrics* 2008; **8**: 24.

44. McManus RJ, Mant J, Haque MS, Bray EP, Bryan S, Greenfield SM, Jones MI, Jowett S, Little P, Penaloza C, Schwartz C, Shackleford H, Shovelton C, Varghese J, Williams B, Hobbs FD, Gooding T, Morrey I, Fisher C, Buckley D. Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized clinical trial. *Jama* 2014; **312**(8): 799-808.

45. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *International journal of clinical pharmacology and therapeutics* 2008; **46**(2): 72-83.

46. National Clinical Guideline C. Hypertension: The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18 and 34. London: Royal College of Physicians (UK); 2011.

47. McManus RJ, Mant J, Bray EP, Holder R, Jones MI, Greenfield S, Kaambwa B, Banting M, Bryan S, Little P, Williams B, Hobbs FD. Telemonitoring and self-management in the control of hypertension (TASMINH2): a randomised controlled trial. *Lancet* 2010; **376**(9736): 163-72.

48. Tucker KL, Sheppard JP, Stevens R, Bosworth HB, Bove A, Bray EP, Godwin M, Green B, Hebert P, Hobbs FDR, Kantola I, Kerry S, Magid DJ, Mant J, Margolis KL, McKinstry B, Omboni S, Ogedegbe O, Parati G, Qamar N, Varis J, Verberk W, Wakefield BJ, McManus RJ. Individual patient data meta-analysis of self-monitoring of blood pressure (BP-SMART). *Journal of Human Hypertension* 2015; **29**(10): 635-.

49. Nathan A, Goodyer L, Lovejoy A, Rashid A. 'Brown bag' medication reviews as a means of optimizing patients' use of medication and of identifying potential clinical problems. *Family practice* 1999; **16**(3): 278-82.

50. Donovan J, Mills N, Smith M, Brindle L, Jacoby A, Peters T, Frankel S, Neal D, Hamdy F. Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. Commentary: presenting unbiased information to patients can be difficult. *BMJ (Clinical research ed)* 2002; **325**(7367): 766-70.

51. Donovan JL, Rooshenas L, Jepson M, Elliott D, Wade J, Avery K, Mills N, Wilson C, Paramasivan S, Blazeby JM. Optimising recruitment and informed consent in randomised controlled trials: the development and implementation of the Quintet Recruitment Intervention (QRI). *Trials* 2016; **17**(1): 283.

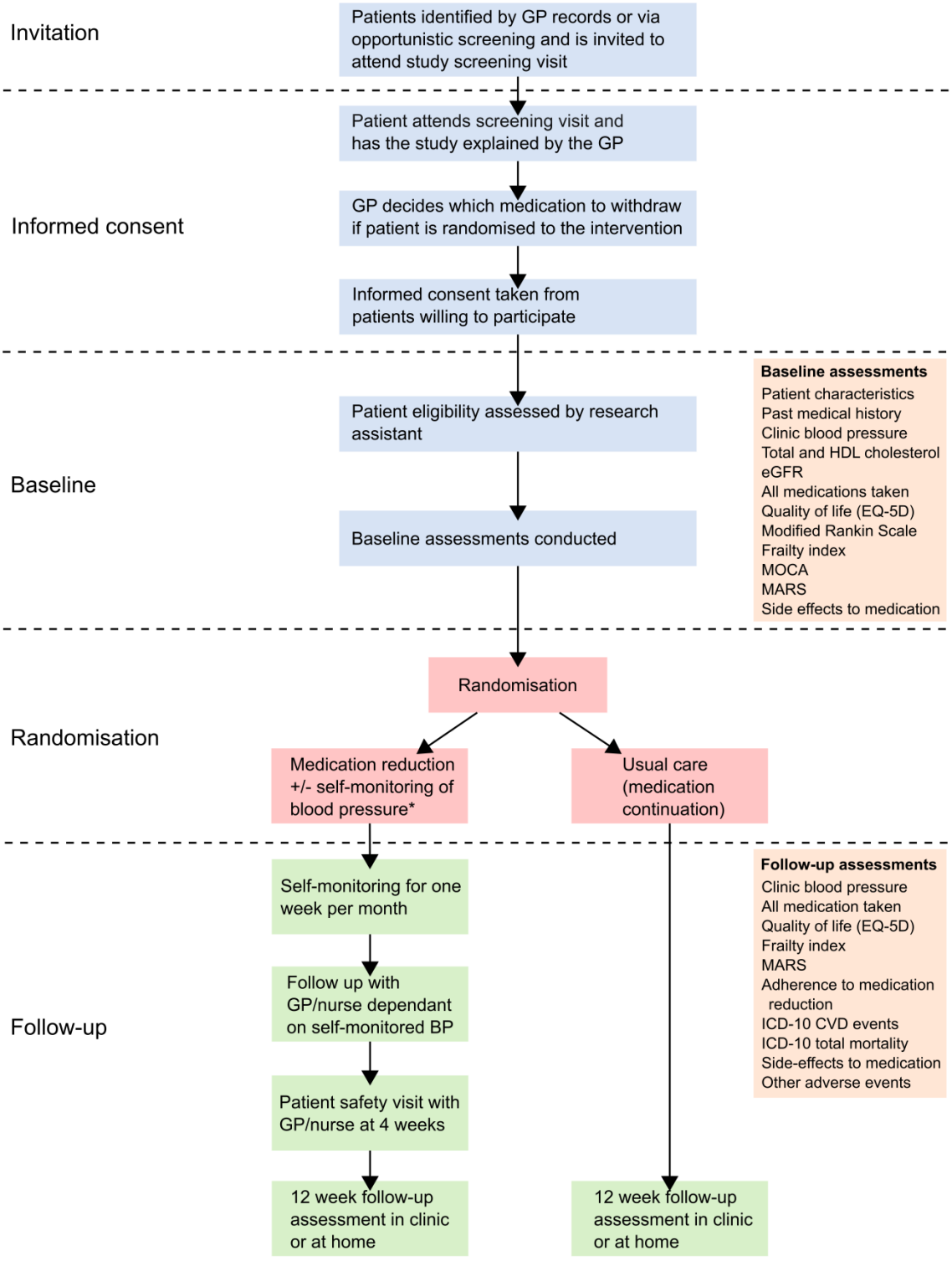
52. Kaambwa B, Bryan S, Jowett S, Mant J, Bray EP, Hobbs FD, Holder R, Jones MI, Little P, Williams B, McManus RJ. Telemonitoring and self-management in the control of hypertension (TASMINH2): a cost-effectiveness analysis. *European journal of preventive cardiology* 2014; **21**(12): 1517-30.

53. Walker E, Nowacki AS. Understanding equivalence and noninferiority testing. *Journal of general internal medicine* 2011; **26**(2): 192-6.

54. Bulpitt CJ, Beckett NS, Cooke J, Dumitrascu DL, Gil-Extremera B, Nachev C, Nunes M, Peters R, Staessen JA, Thijs L. Results of the pilot study for the Hypertension in the Very Elderly Trial. *Journal of hypertension* 2003; **21**(12): 2409-17.

55. Warwick J, Falaschetti E, Rockwood K, Mitnitski A, Thijs L, Beckett N, Bulpitt C, Peters R. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the HYpertension in the Very Elderly Trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over. *BMC medicine* 2015; **13**: 78.

21. APPENDIX A: TRIAL FLOW CHART



*Monitoring of blood pressure at home will be encouraged but those not willing or able will still be included in the trial. All patient will be asked to attend a safety monitoring visit with their GP/nurse four weeks after baseline.
GP = General practitioner; BP = Blood pressure; HDL = High density lipoprotein; ICD = International Statistical Classification of Diseases and Related Health Problems; CVD = Cardiovascular disease; eGFR = estimated Glomerular Filtration Rate (eGFR); MARS = Medication Adherence Rating Scale; MOCA = Montreal Cognitive Assessment

22. APPENDIX B: DATA COLLECTION SOURCES AND SCHEDULE

No.	Variable	From medical notes	Measured at clinic	Recorded at Baseline	Recorded at Follow-up
1	Age		✓	✓	
2	Sex		✓	✓	
3	Ethnicity		✓	✓	
4	Marital status		✓	✓	
5	Education		✓	✓	
6	Duration of hypertension	✓		✓	
7	Past medical history	✓		✓	
8	Alcohol consumption		✓	✓	✓
9	Smoking		✓	✓	✓
10	Height		✓	✓	✓
11	Weight		✓	✓	✓
12	Clinic blood pressure (sitting and standing)		✓	✓	✓
13	Cholesterol (total and HDL)	✓		✓	
14	estimated Glomerular Filtration Rate (eGFR)	✓		✓	
15	Prescribed or over the counter medications (all medications)*	✓	✓	✓	✓
16	Quality of life (according to EQ-5D-5L)[35]		✓	✓	✓
17	Functional independence (defined by modified Rankin Scale)[37]		✓	✓	
18	Frailty (according to the FRAIL scale)[36]		✓	✓	✓
19	Frailty (according to the frailty index and electronic frailty index)[31, 39]	✓	✓	✓	✓
20	Cognitive function (defined by the Montreal Cognitive Assessment [MoCA])[40]		✓	✓	
21	Adherence to medication (according to the Medication Adherence Rating Scale (MARS) Questionnaire)[41]		✓	✓	✓
22	Adherence to medication reduction		✓		✓
23	ICD-10 coded Cardiovascular events and mortality during the trial	✓			✓
24	Recording of potential side effects to medication		✓	✓	✓
25	Recording of adverse events	✓	✓		✓

HDL = High density lipoprotein; ICD = International Statistical Classification of Diseases and Related Health Problems

*Drug substance/name, formulation, dose, frequency, start date and adherence over past 12 months (according to clinical system)

23. APPENDIX C: ITEMS INCLUDED IN FRAILTY INDEX ASSESSMENT

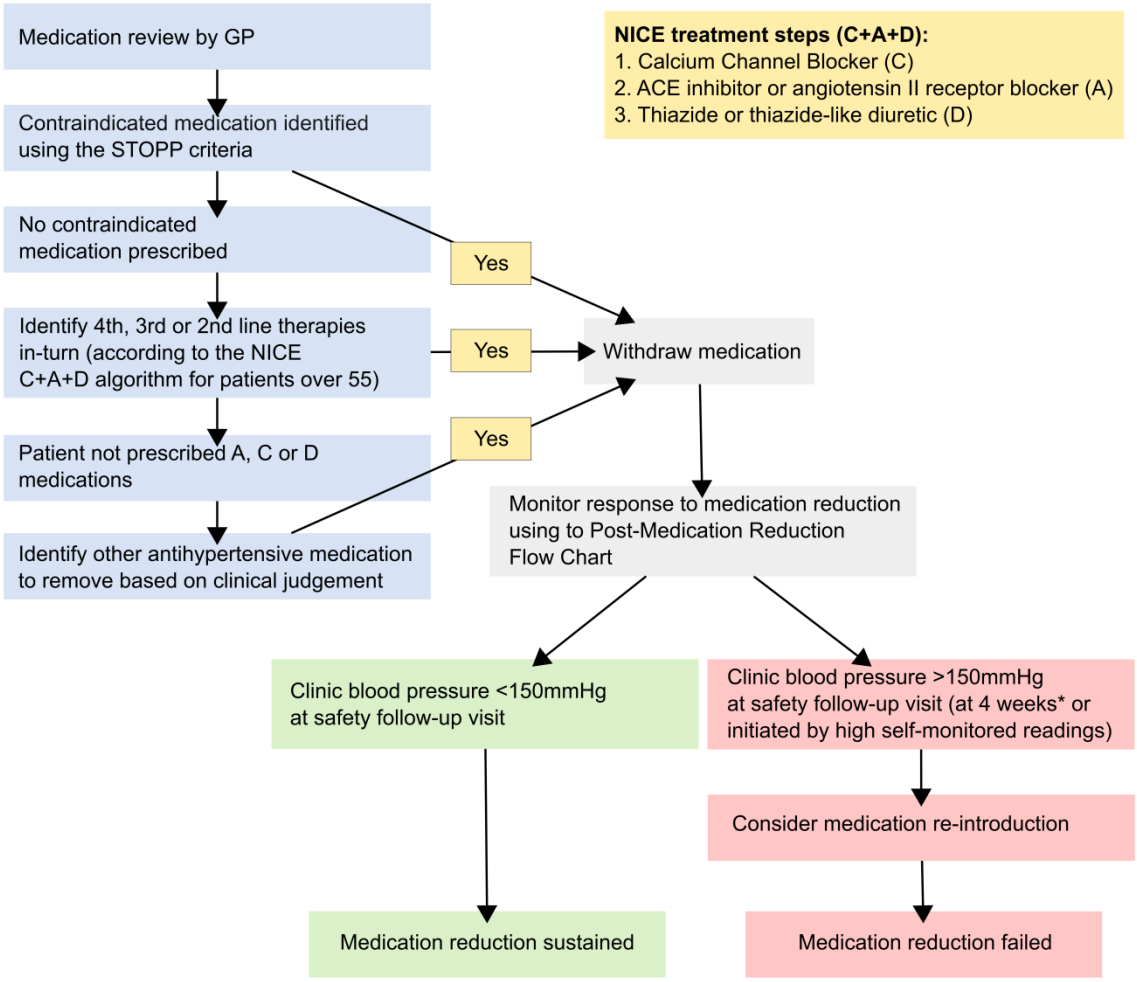
Adapted from Searle *et al.,* and Clegg *et al.* (the original Frailty Index and electronic Frailty Index),[31, 43] Morley *et al.* (the FRAIL Scale),[36] the HYVET[54, 55] and OPTIMED trials. Items permit estimation of frailty according to the original frailty index (FI; for comparison with SPRINT and HYVET trials),[43] the electronic frailty index (eFI)[31] and the frail scale (FS).[36]

No.	Item	Source	Deficit type	Coding	Routine data	Patient data	FI	eFI	FS
1.	Activities prevented by pain/discomfort	OPTIMED	Symptom	Yes (1), No (0)	✓		✓	✓	
2.	Alzheimer's Disease or other dementia	OPTIMED	Disease	Yes (1), No (0)	✓		✓		
3.	Angina	Morley	Disease	Yes (1), No (0)	✓		✓	✓	✓
4.	Any fall in the past month	New	Symptom	Yes (1), No (0)		✓	✓		
5.	Arthritis or rheumatism	Searle et al.,	Disease	Yes (1), No (0)	✓		✓	✓	✓
6.	Asthma	Morley	Disease	Yes (1), No (0)	✓		✓		✓
7.	Atrial Fibrillation	Clegg et al.,	Disease	Yes (1), No (0)	✓		✓	✓	
8.	Autoimmune disease	OPTIMED	Disease	Yes (1), No (0)	✓		✓		
9.	Back pain (excluding arthritis)	OPTIMED	Symptom	Yes (1), No (0)	✓		✓		
10.	Bowel disorder including faecal incontinence	OPTIMED	Disease	Yes (1), No (0)	✓		✓		
11.	Cancer	Searle et al.,	Disease	Yes (1), No (0)	✓		✓		✓
12.	Chronic Kidney disease	Morley	Disease	Yes (1), No (0)	✓		✓	✓	✓
13.	Chronic lung disease	Searle et al.,	Disease	Yes (1), No (0)	✓		✓	✓	✓
14.	Cognition problems (but no dementia diagnosed)	OPTIMED	Disability	Yes (1), No (0)	✓		✓	✓	
15.	Derived trouble with vision	OPTIMED	Disability	Yes (1), No (0)	✓		✓	✓	
16.	Dexterity problems	OPTIMED	Disability	Yes (1), No (0)	✓		✓		
17.	Diabetes	Searle et al.,	Disease	Yes (1), No (0)	✓		✓	✓	✓
18.	Difficulty walking 10 steps without aids or resting (resistance)	Morley	Disability	Yes (1), No (0)		✓	✓		✓
19.	Difficulty walking 100 yards without aids (ambulation)	Morley	Disability	Yes (1), No (0)		✓	✓		✓
20.	Dizziness	Clegg et al.,	Symptom	Yes (1), No (0)	✓		✓	✓	

21.	Dyspnoea	Clegg et al.,	Symptom	Yes (1), No (0)	✓		✓	✓	
22.	Emotional problems	OPTIMED	Disability	Yes (1), No (0)	✓		✓		
23.	Epilepsy	OPTIMED	Disease	Yes (1), No (0)	✓		✓		
24.	Fall resulting in hospitalisation	New	Symptom	Yes (1), No (0)	✓		✓	✓	
25.	Feeling depressed	Searle et al.,	Symptom	Most of the time (1), sometimes (0.5), rarely (0)		✓	✓		
26.	Feeling lonely	Searle et al.,	Symptom	Most of the time (1), sometimes (0.5), rarely (0)		✓	✓		
27.	Feeling tired a lot of the time (fatigue)	Morley	Symptom	1 = All of the time, 0.75 = Most of the time, 0.50 = Some of the time, 0.25 = A little of the time, 0 = None of the time		✓	✓		✓
28.	Foot problems	Clegg et al.,	Disease	Yes (1), No (0)	✓		✓	✓	
29.	Fragility fracture	Clegg et al.,	Disease	Yes (1), No (0)	✓		✓	✓	
30.	Haematological disorders (anaemia, CML etc.)	OPTIMED	Disease	Yes (1), No (0)	✓		✓	✓	
31.	Hearing problems	OPTIMED	Disability	Yes (1), No (0)	✓		✓	✓	
32.	Heart failure	Searle et al.,	Disease	Yes (1), No (0)	✓		✓	✓	✓
33.	Heart valve disease	Clegg et al.,	Disease	Yes (1), No (0)	✓		✓	✓	
34.	High BP or hypertension or treated BP	Searle et al.,	Disease	Yes (1), No (0)	✓		✓	✓	✓
35.	Housebound	Clegg et al.,	Disability	Yes (1), No (0)	✓		✓	✓	
36.	Hypotension/syncope	Clegg et al.,	Disease	Yes (1), No (0)	✓		✓	✓	
37.	Loss of weight in the past year	Morley	Symptom	≥5% (1), <5% (0)	✓		✓	✓	✓
38.	Mobility problems	OPTIMED	Disability	Yes (1), No (0)	✓		✓	✓	
39.	Needing help bathing	Searle et al.,	Disability	Yes (1), No (0)		✓	✓		
40.	Needing help for housework	Searle et al.,	Symptom	Yes (1), No (0)		✓	✓		
41.	Needing help getting in and out of a chair	Searle et al.,	Disability	Yes (1), No (0)		✓	✓		
42.	Needing help in moving about the house	Searle et al.,	Symptom	Yes (1), No (0)		✓	✓		
43.	Needing help taking medication	Searle et al.,	Symptom	Yes (1), No (0)		✓	✓		
44.	Orthostatic Hypertension	HYVET	Symptom	Yes (1), No (0)	✓		✓		
45.	Osteoporosis	Clegg et al.,	Disease	Yes (1), No (0)	✓		✓	✓	

46.	Overwright or obese	HYVET	Symptom	BMI <25 (0), ≥25 but <30 (0.5), ≥30 (1)	✓		✓		
47.	Parkinsonism and tremor	Clegg et al.,	Disease	Yes (1), No (0)	✓			✓	
48.	Peripheral vascular disease	Clegg et al.,	Disease	Yes (1), No (0)	✓			✓	
49.	Polypharmacy	Clegg et al.,	Sign	Yes (1), No (0)	✓			✓	
50.	Previous Myocardial Infarction	Searle et al.,	Disease	Yes (1), No (0)	✓		✓	✓	✓
51.	Previous stroke	Searle et al.,	Disease	Yes (1), No (0)	✓		✓	✓	✓
52.	Receiving home care services	OPTIMED	Symptom	Yes (1), No (0)	✓	✓	✓	✓	
53.	Self-rating of Health	Searle et al.,	Symptom	Poor (1), Fair (0.75), Good (0.5), Very Good (0.25), Excellent (0)		✓	✓		
54.	Skin ulcers	OPTIMED	Disease	Yes (1), No (0)	✓		✓	✓	
55.	Sleep disturbance	Clegg et al.,	Sign	Yes (1), No (0)	✓			✓	
56.	Social vulnerability	Clegg et al.,	Disability	Yes (1), No (0)	✓			✓	
57.	Stomach or intestinal ulcers	OPTIMED	Disease	Yes (1), No (0)	✓		✓	✓	
58.	Thyroid condition or treatment	OPTIMED	Disease	Yes (1), No (0)	✓		✓	✓	
59.	Urinary incontinence	HYVET	Symptom	Yes (1), No (0)	✓		✓	✓	
60.	Urinary system disease	Clegg et al.,	Disease	Yes (1), No (0)	✓			✓	

24. APPENDIX D: MEDICATION REDUCTION ALGORITHM



Initial safety follow-up visit may vary depending drug removed or the side effects experienced – see post medication reduction monitoring flow chart (Appendix E).

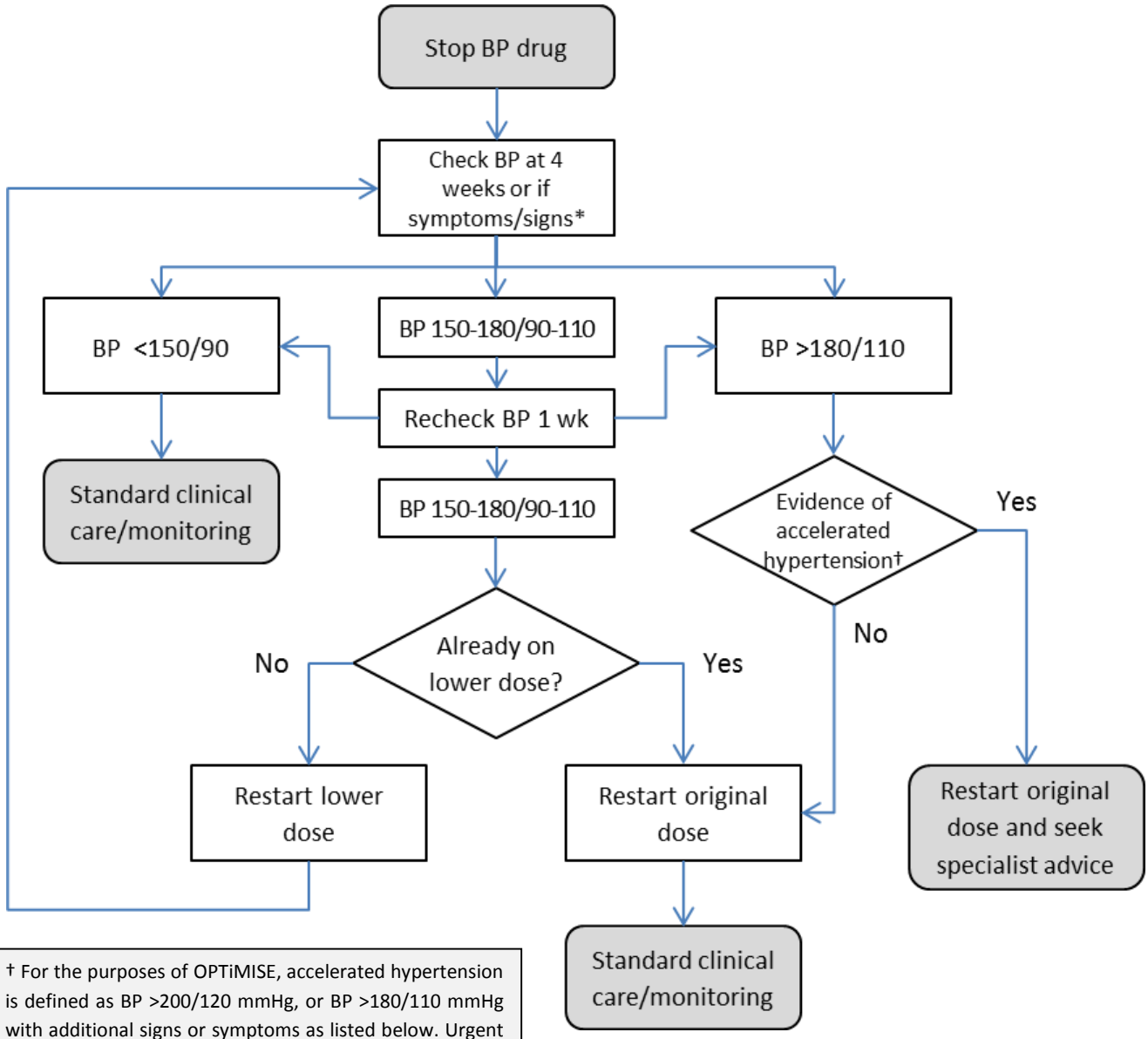
STOPP criteria[45]

Withdraw the one of the following medications if any of the ensuing contraindications are identified:

- Thiazide diuretic with a history of gout (may exacerbate gout).
- Beta-blocker in combination with verapamil (risk of symptomatic heart block).
- Non-cardioselective beta-blocker with chronic obstructive pulmonary disease (risk of bronchospasm).
- Calcium channel blockers with chronic constipation (may exacerbate constipation).
- Use of diltiazem or verapamil with NYHA Class III or IV heart failure (may worsen heart failure).

25. APPENDIX E: POST MEDICATION REDUCTION MONITORING FLOW CHART

- The full effects of most oral antihypertensives can last for up to 4-6 weeks. Frequent monitoring in the initial 4 weeks after drug withdrawal is thus not required unless BP levels are extreme or there are other clinical concerns (see below).
- Where systolic/diastolic BP values fall into different categories, consider the higher value
- BP should be taken as the averaged second and third measurements using a validated monitor
- Standard clinical care/monitoring should align with NICE recommendations[46]



† For the purposes of OPTiMISE, accelerated hypertension is defined as BP >200/120 mmHg, or BP >180/110 mmHg with additional signs or symptoms as listed below. Urgent (same day) expert opinion should be sought.

- 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

*Signs and symptoms directly related to elevated BP are not anticipated, but BP should 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)

26. APPENDIX F: SELF-MONITORING PROTOCOL (TRAFFIC LIGHT SYSTEM)

UNDERSTANDING YOUR MEASUREMENTS

For patients 80 years and over

For RED or BLUE readings you will need to repeat them initially and if they remain too high or too low you will be advised to seek medical advice.

In each case, the top reading is the SYStolic and bottom reading DIAstolic.

Colour	Level	Blood Pressure	Action
RED	**HIGH**	**SYS 171 or more OR DIA 106 or more**	**Your BP is too high.** Make an appointment within 48 hours to see your GP or nurse.
AMBER	**RAISED** your GP/nurse may contact you to alter your medication	**SYS 146-170 OR DIA 86-105**	**Your BP is raised.** If you have persistent AMBER readings (4 or more days of the week) then you should contact from your GP/Practice nurse as you may need your medication altered.
GREEN	**NORMAL**	**SYS 100-145 AND DIA 85 or less**	**Your BP is normal.** This is fine provided that you have no side effects.
BLUE	**LOW**	**SYS 99 or less**	**Your BP is too low.** Make an appointment within 48 hours to see your GP or nurse.

27. APPENDIX G: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	13.01.2017	Sheppard, J.; McManus, R.; Temple, E.	The expectedness of SARs must be assessed more appropriately in the context of this trial. The expectedness of adverse events occurring as a result of re-introduction of withdrawn medication will be determined according to the latest version of the Summary of medicinal Product Characteristics (SmPC, section 4.8). There are no sections of the SmPC, or previous clinical studies which detail expected adverse events as a result of medication withdrawal (the study IMP) and therefore all SAEs at least possibly related, and not as a result of re-introduction of withdrawn medication, will be considered unexpected and reported as SUSARs. This replaces wording that SAEs will not be assessed for expectedness. The definition of SUSAR was also clarified in Section 12.1 for the context of this trial. Unclear definitions of adverse events were also removed to avoid confusion. It was also clarified that adverse events that are observed by the Investigator or reported by the participant may be reported at any time.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.