

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

OPTimising Treatment for MIld Systolic hypertension in the Elderly (OPTiMISE): protocol for a randomised controlled non-inferiority trial

| | |
|--|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2018-022930 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 13-Mar-2018 |
| Complete List of Authors: | <p>Sheppard, James; University of Oxford, Nuffield Department of Primary Care Health Sciences</p> <p>Burt, Jenni; University of Cambridge, Cambridge Centre for Health Services Research</p> <p>Lown, Mark; University of Southampton</p> <p>Temple, Eleanor; University of Oxford, Nuffield Department of Primary Care Health Sciences</p> <p>Benson, John; University of Cambridge, GP and Primary Care Research Unit</p> <p>Ford, Gary; Oxford University Hospitals NHS Foundation Trust, Oxford Academic Health Science Network</p> <p>Heneghan, Carl; Oxford University, Primary Health Care</p> <p>Hobbs, Richard; University of Oxford, Nuffield Department of Primary Care Health Sciences</p> <p>Jowett, Sue; University of Birmingham, Health Economics Unit</p> <p>Little, Paul; University of Southampton, Primary Care and Population Science;</p> <p>Mant, Jonathan; University of Cambridge, General Practice and Primary Care Research Unit</p> <p>Mollison, Jill; University of Oxford, Nuffield Department of Primary Care Health Sciences</p> <p>Nickless, Alecia; University of Oxford, Nuffield Department of Primary Care Health Sciences</p> <p>Ogburn, Emma; University of Oxford,</p> <p>Payne, Rupert; University of Bristol, Centre for Academic Primary Care</p> <p>Williams, Marney; Patient and public involvement representative</p> <p>Yu, Ly-Mee; University of Oxford, Department of Primary Care Health Sciences</p> <p>McManus, Richard; University of Oxford, Dept of Primary Care Health Sciences</p> |
| Keywords: | Multi-morbidity, Cardiovascular disease, Frailty, Antihypertensive, De-prescribing |
| <p>Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.</p> <p>OPTiMISE video infographic V1.1 14.03.17.mp4</p> | |

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

SCHOLARONE™
Manuscripts

For peer review only

1
2
3
4
5
6
7
8
9

Optimising Treatment for Mild Systolic hypertension in the Elderly (OPTiMISE): protocol for a randomised controlled non-inferiority trial

10
11
12
13
14
15
16
17
18
19

James P Sheppard,¹ Jenni Burt,² Mark Lown,³ Eleanor Temple,¹ John Benson,⁴ Gary A Ford,¹ Carl Heneghan,¹ FD Richard Hobbs,¹ Sue Jowett,⁵ Paul Little,³ Jonathan Mant,⁴ Jill Mollison,¹ Alecia Nickless,¹ Emma Ogburn,¹ Rupert Payne,⁶ Marney Williams,⁷ Ly-Mee Yu,¹ and Richard J McManus¹

20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

¹Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

²The Healthcare Improvement Studies Institute, University of Cambridge, Cambridge, UK

³Primary Care Research Group, University of Southampton, Southampton, UK

⁴Primary Care Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

⁵Institute of Applied Health Research, University of Birmingham, Birmingham, UK

⁶Centre for Academic Primary Care, University of Bristol, Bristol, UK

⁷Patient and public involvement representative, London, UK

Corresponding author: James P Sheppard

Email: james.sheppard@phc.ox.ac.uk

Telephone: +44 1865 617192

Address: Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, University of Oxford, Oxford, OX2 6GG, UK

Trial Sponsor: University of Oxford

Contact name: 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

Word count: 4,208 (excluding title page, abstract, references, tables and figures)

Number of tables: 2

Number of figures: 3

Abstract

Introduction: Recent evidence suggests that larger blood pressure reductions and multiple antihypertensive drugs may be harmful in older people, particularly frail individuals with polypharmacy and multi-morbidity. However, there is a lack of evidence to support de-prescribing of antihypertensives, which limits the practice of medication reduction in routine clinical care. The aim of this trial is to examine whether antihypertensive medication reduction is possible in older patients without significant changes in blood pressure control at follow-up.

Methods and analysis: This trial will use a Primary Care based, open label, randomised controlled trial design. A total of 540 participants will be recruited, aged ≥ 80 years, with systolic blood pressure < 150 mmHg and receiving ≥ 2 antihypertensive medications. Participants will have no compelling indication for medication continuation and will be considered to potentially benefit from medication reduction due to existing polypharmacy, co-morbidity and frailty. Following a baseline appointment, individuals will be randomised to a strategy of medication reduction (intervention) with optional self-monitoring or usual care (control). Those in the intervention group will have one antihypertensive medication stopped. The primary outcome will be to determine if a reduction in medication can achieve a proportion of participants with clinically safe blood pressure levels at 12 week follow-up (defined as a systolic blood pressure < 150 mmHg) which is non-inferior (within 10%) to that achieved by the usual care group. Qualitative interviews will be used to understand the barriers and facilitators to medication reduction. The study will use economic modelling to predict the long term effects of any observed changes in blood pressure and quality-of-life.

Ethics and dissemination: The protocol and written information has been approved by a Research Ethics Committee, medicines regulatory authority (MHRA), and national and local health research authorities. All research outputs will be published in peer-reviewed journals and presented at national and international conferences.

Trial registration: EudraCT 2016-004236-38

Word count: 299 (max 300)

Keywords: Multi-morbidity, cardiovascular disease, frailty, antihypertensive, de-prescribing

Strengths and weaknesses of this study

- This will be the first UK randomised controlled trial to compare a strategy of antihypertensive medication reduction to usual care in primary care.
- The pragmatic trial design, with broad inclusion criteria, will make findings of the study externally valid in routine clinical practice.
- Allowing the attending GP to choose the medication to be reduced will maximise external validity of the trial results but precludes the possibility of blinding the participants and investigators.
- The trial will be powered to detect a non-inferior difference in blood pressure control at follow-up, but not necessarily secondary outcomes such as differences in rates of cardiovascular disease, adverse events and quality of life.

For peer review only

Introduction

The general population is ageing¹ and, consequently, the number of people living with age-related chronic conditions is increasing.² Hypertension is the number one co-morbid condition in older people with multiple chronic conditions³ and 52% of those aged ≥ 80 years are prescribed two or more antihypertensive drugs (equivalent to approximately 1.25 million people in the UK).⁴ 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 >160 mmHg) and high risk stage 1 hypertension.^{5,6} However, as with many trials,^{7,8} these studies included healthier populations with lower polypharmacy and multi-morbidity than might be expected in the general elderly population. In addition, there is evidence to suggest that larger blood pressure reductions and multiple antihypertensive prescriptions may be harmful in older people.^{9,10} Evidence from observational studies also suggests that higher intensity blood pressure treatment is associated with increased risk of falls in older people,¹¹ although this is also disputed.⁵

Some patients consider the increased risk of falls and other adverse events to be as important as the risk of myocardial infarction or stroke, particularly those taking medications for primary prevention of cardiovascular disease.¹² Thus, decisions over blood pressure lowering in the elderly, particularly the frail elderly, require the weighing of harms and quality of life. However, clinicians can often struggle to stop prescribing medication due to a perceived lack of evidence, fear of the reaction of other prescribers, fear of precipitating events such as stroke or angina and concern that patients will feel their care is being cut.^{13,14}

There is limited evidence from randomised trials examining the safety of antihypertensive medication reduction or withdrawal.¹⁵⁻¹⁹ The HYVET trial⁵ enrolled some patients on antihypertensive treatment who were then randomised to placebo (effectively complete medication withdrawal), but there are few trials comparing a specified strategy of antihypertensive medication reduction with usual care in terms of effects on blood pressure control and quality of life.¹⁷ In addition, there are no previous economic modelling studies of a strategy of medication reduction in the elderly.

The aim of this work will be to examine whether antihypertensive medication reduction in patients with controlled systolic hypertension (≤ 150 mmHg) who are being prescribed two or more antihypertensives is possible without significant changes in blood pressure control at follow-up.

Methods

Aims and outcomes

The aim of this study is to determine whether antihypertensive medications can be safely reduced without systolic blood pressure increasing beyond clinically safe levels at follow-up.

The primary outcome is the proportion of participants with clinically safe levels at 12 week follow-up (defined as a systolic blood pressure <150 mmHg) Secondary outcomes will examine:

- The proportion of participants in the intervention arm who maintain medication reduction through to follow-up (*i.e.* are *not* restarted on therapy).
- The difference in quality of life (according to EQ-5D-5L) between groups at 12 week follow-up.
- The difference in frailty (according to the frailty index)²⁰ between the two groups at 12 week follow-up.
- The difference in the change in mean clinic systolic blood pressure (from baseline) between the two groups at 12 week follow-up.
- The difference in reported side effects to medication between the two groups at 12 week follow-up (including coughs, dizziness, syncope, and ankle swelling).

- 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).

Design

This trial will use a Primary Care based, open label, randomised controlled, two-parallel groups, non-inferiority trial design, recruiting 540 participants with controlled blood pressure (systolic <150 mmHg) on two or more antihypertensive treatments. Participants will be randomised to a strategy of medication reduction (intervention) or usual care (control) and followed-up for 12 weeks (see figure 1). Embedded qualitative and economic analyses will examine barriers and facilitators to medication reduction and the cost effectiveness of the approach.

Trial participants

Patients eligible for the trial will be aged ≥ 80 years, with systolic blood pressure <150mmHg (current UK guideline recommendation)²¹ receiving ≥ 2 antihypertensive medications. They will have no compelling indication for medication continuation and in the opinion of the attending GP, may potentially benefit from medication reduction due to existing polypharmacy, co-morbidity and/or frailty (table 1).

Participants will be identified and recruited from general practices via the UK Clinical Research Network (CRN). Potentially eligible patients will be identified by trained practice staff searching practice-based electronic disease registers using a standardised strategy. GPs will be asked to check the search results and remove people whom they believe to be unsuitable to participate in the study. Remaining potentially eligible patients will be sent letters of invitation from their GP and those expressing an interest in the trial will be asked to attend a screening and baseline appointment. Patients not responding to the first invitation will receive one reminder letter (up to four weeks after the first letter). Other potentially eligible patients may also be approached opportunistically by a member of the clinical care team. Those who do not wish to take part will be asked to fill in a short questionnaire detailing their reasons.

Baseline visit

Eligible patients will have informed consent taken by the GP. During the consent appointment, the GP will show a two-minute study video infographic (see supplementary material) and go through the participant information sheet explaining the exact nature of the trial. Having had a chance to ask questions, those individuals willing to participate will give written informed consent by means of a participant dated signature and dated signature of the GP who presented and obtained the informed consent.

Some participants will be invited to have their interview audio-recorded for qualitative analysis during their study visits. Those who are interested will be asked to sign a response slip prior to meeting the GP. Consent to audio recordings will not have a bearing on an individual's care or eligibility for the main trial.

Those giving informed consent will be screened using the criteria in table 1 and undergo baseline measurements by a member of the research team via participant questionnaires and a detailed notes review (table 2). Blood pressure will be measured in a standardised fashion using the clinically validated²² BpTRU blood pressure monitor which automatically records six blood pressure measurements at one minute intervals. Blood pressure readings will be taken in the left arm (where appropriate) after participants have been seated for at least five minutes of rest, using an appropriate sized cuff. The mean of the 2nd and 3rd readings will be used to define the primary outcome. To test for orthostatic hypotension, two further readings will be taken in the standing position after one and three minutes.²³ Orthostatic

hypotension will be defined as a ≥ 20 mmHg drop in systolic blood pressure within three minutes of standing.

All data will be collected via an electronic case report form (eCRF) linked to the study database. Participants will be given the option to enter responses to questionnaires themselves or with assistance from the research team. Where questionnaires are not validated for use on a tablet computer,²⁴ or where individuals are not comfortable using one, paper copies will be made available for completion.

Randomisation

Consenting participants will be individually randomised (1:1 allocation ratio) to one of two study arms using a fully validated web-based system (Sortition®) with manual telephone back up. Participants will not be randomised until after consent has been taken and baseline assessments have been completed. A computer generated non-deterministic algorithm, minimising on practice and baseline systolic blood pressure will be used to ensure these covariates are balanced between the two intervention arms.

The study will use an open label design, so patients and practitioners will not be blinded to the intervention or study endpoints. Therefore, codebreaking will not be necessary. The statistical analysis will be performed blind to patient allocation.

Intervention group

Participating GPs will review each participant's antihypertensive medication regimen prior to the baseline appointment, and decide which medication should be removed if they are randomised to the intervention arm of the trial. The choice of medication to be withdrawn will be at the discretion of the GP, but their decision will be informed by an individual's co-morbidities and existing guidelines, where appropriate (figure 2). Specifically, participating GPs will be encouraged to identify previously unrecognised contraindications to medication, defined by the STOPP criteria.²⁵ In the absence of these, or a strong clinical rationale for continuing despite a STOPP criteria being met, GPs will be recommended to reduce antihypertensive medications in reverse of the NICE C+A+D algorithm for older patients (figure 2).²¹ All participants in the trial will remain on at least one antihypertensive.

Once a medication has been removed, GPs or other appropriate, delegated healthcare professionals will closely monitor the participant's response to medication reduction: they will be given advice about what and when to monitor (figure 3), but this schedule will be flexible. All participants will be expected to return for at least one routine safety follow-up visit, and further visits may be required if blood pressure is raised (≥ 150 mmHg), or adverse events occur. Where blood pressure is persistently raised, GPs will be expected to re-adjust medication (dose or type), rendering the likelihood of a serious adverse event occurring as a result of the intervention very low.

Self-monitoring

All participants randomised to the medication reduction arm of the trial will be given the option to self-monitor their blood pressure at home. Those accepting will be trained using protocols developed in the previous TASMIN trials^{26 27} and will be given simple and clear instructions to contact their GP if their blood pressure rises above what is considered clinically safe (e.g. home systolic blood pressure > 145 mmHg on all readings taken in a week). Participants will be advised 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

1 control group (many patients now self-monitor routinely)²⁸ is not expected to impact on the study results,
2 since there is good evidence that self-monitoring only affects blood pressure levels if used in combination
3 with a co-intervention.²⁹ All other clinical care will continue as usual.
4
5

6 *Control group*

7 Those allocated to the control arm of the study will continue usual clinical care (i.e. they will continue to
8 take antihypertensive medications as prescribed and will not self-monitor unless already doing so). No
9 other medication changes will be mandated and participating GPs will be asked to manage all other care
10 according to usual clinical practice.
11
12

13 *Follow-up visits*

14 Participants will attend one research follow-up clinic, 12 weeks (± 2 weeks) after baseline and those in the
15 intervention will attend one additional safety visit after four weeks (± 2 weeks) (figure 1). A period of four
16 weeks is expected to be sufficiently long enough to assess the impact of antihypertensive medication
17 reduction, since these drugs usually take approximately four weeks to 'wash out' of a patient's system.
18 Earlier safety visits are not recommended since they could provide false reassurance that blood pressure is
19 within safe limits if the withdrawn drug has not washed out of the participant's system.
20
21
22

23 The follow-up assessments will include standardised blood pressure measurement (for assessment of the
24 primary outcome), questionnaire assessments and adherence to the trial medication regime, side effects
25 and adverse events (table 2). Where possible, all participants will be flagged for mortality and hospital
26 admissions using NHS patient tracking services, permitting long-term follow-up for up to 5 years after the
27 trial has finished.
28
29

30 Each participant has the right to withdraw from the trial at any time. We will ask all participants to attend a
31 follow-up visit as far as is practicable, regardless of whether medication is re-introduced to participants in
32 the intervention group, or a participant in the control group has medication withdrawn. Unless a
33 participant withdraws consent, vital status will be assessed even where an individual has been lost to
34 follow-up (for instance moved away). If given, the reason for withdrawal will be recorded in the eCRF.
35
36
37

38 *Internal feasibility study*

39 A two-stage internal feasibility study will be conducted to examine methods of patient invitation and rates
40 of recruitment, before proceeding with the main trial. The first feasibility phase will last for a minimum of
41 three months and aim to recruit approximately 25 participants from a minimum of 3-5 practices. The aim
42 will be to establish whether or not anyone will be willing to participate in the study.
43
44

45 The second feasibility phase will focus on recruitment rates for the main trial and whether the intended
46 sample size is likely to be met during the recruitment period. This phase will have a recruitment target of 75
47 participants from ten practices over 6 months, giving a total sample for the feasibility study of 100
48 participants. A recruitment rate of 15% of invitations sent is expected. The following actions will be
49 considered to address varying rates of recruitment at the end of the feasibility phases:
50

- 51 - If ≥ 100 participants are recruited – trial will proceed as planned
 - 52 - If 75-99 participants are recruited – recruitment materials/method will be re-examined and edited
53 where necessary following discussions with stakeholders and patient and public involvement
54 representatives.
55
- 56
57
58
59
60

- If 50-74 participants are recruited – the allocation of resources and recruitment criteria will be re-examined using information gathered from concurrent qualitative work.
- If <50 participants 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.

Sample size calculation

Assuming that 100% of participants 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 participants will be required to detect a non-inferior difference in systolic blood pressure control between groups. Calculations assume a 10% non-inferiority margin, 90% power, 2.5% 1-sided level of significance, 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 this type of trial, but 10% was deemed useful 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, at least nine will still have controlled blood pressure at 12 week follow-up.

Statistical analysis

A detailed statistical analysis plan will be agreed prior to the end of the trial. The primary and secondary analyses will be by intention to treat (ITT), unless stated otherwise. The primary analysis will be a non-inferiority analysis by means of the “two one-sided test” (TOST) procedure,³⁰ whereby the 95% confidence interval for the relative risk of participants with systolic blood pressure at 12 weeks below 150 mmHg between the medication reduction group and the usual care group is calculated. This will be obtained by means of a generalised linear mixed effects model with GP surgery included as a random effect and baseline blood pressure as a fixed effect. 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 be non-inferior in terms of blood pressure control to usual care will be accepted. As a secondary analysis of the primary outcome, a per-protocol (PP) analysis will be performed, since ITT can be anticonservative for a non-inferiority hypothesis.³⁰ 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.

Secondary analyses will examine the proportion of participants in the medication reduction arm who maintained their medication reduction throughout the 12 week follow-up period. Secondary outcomes will be analysed by means of linear mixed effects models, 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.

Patient and public involvement

This protocol was developed through discussions with older patients and carers and members of an AgeUK day centre. MW is a stroke survivor with experience as a volunteer on the elderly ward of Charing Cross Hospital. She was consulted on the suitability and design of the trial and is a member of the trial management group. Methods of patient approach, including the design of the video infographic, patient information sheet and consent form were all reviewed by patient representatives prior to formal approval. The TSC includes two independent patient representatives responsible for overseeing the conduct of the trial.

Safety reporting

Adverse events that are observed by an investigator or reported by the participant will be recorded on the AE log at any time during the study but AEs will be specifically asked about at the 12 week follow up. Serious adverse events (SAEs) will be reported to the coordinating centre within 24 hours of discovery or notification of the event. All SAE reports will be reviewed by the DMEC chair on a monthly basis, and by the full DMEC at meetings held every 6 months. The DMEC will include a geriatrician, statistician and consultant clinical pharmacologist. They will be responsible for safeguarding trial participants, monitoring emerging trial data including identifying any trends, such as increases in unexpected events, and take appropriate action where necessary.

All adverse events labelled possibly, probably or definitely related will be considered as related to the intervention. Since there are no sections of the Summary of Medicinal Product Characteristics, or previous clinical studies which detail expected adverse events as a result of medication withdrawal, 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. Fatal and life-threatening SUSARs will be reported by the chief investigator to the relevant Competent Authority and Research Ethics Committee no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. All other SUSARs will be reported within 15 calendar days.

Qualitative sub-studies

Study 1: interviews with doctors and patient

Face-to-face interviews with GPs and patients will be conducted to generate understanding about the barriers and facilitators to antihypertensive medication reduction. Informed consent will be sought from approximately 15 GPs to provide a broad range of opinion from varying practice sizes (small to large) and settings (rural to urban). Participating GPs will also be asked to identify up to 15 patients for interview, based on the same inclusion criteria as those applied to participants in the main trial.

Interviews with GPs will use a chart-stimulated recall approach to explore the factors which influence their treatment choices in older hypertensive patients. Anonymised electronic health records will be used to focus discussions about how GPs would feel about reducing antihypertensive medications. Interviews with patients will use 'brown bag' medication review techniques³¹ to create a complete record of medication held, with a commentary on usage from the participants' perspective. Diagrammatic elicitation techniques will be used to complete a relational map outlining participants' circumstances and how these relate to the medications taken. 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.

1 All interviews will be transcribed verbatim, stored and organised using NVivo software (QSR International
2 Pty Ltd, Doncaster, Victoria, Australia). Interview and visual data from GP and patient interviews will be
3 subjected to thematic analysis, with a particular orientation to exploring clinical and patient perspectives
4 on the barriers and facilitators to reducing antihypertensives.
5
6

7 *Study 2: Assessment of trial recruitment and data collection procedures*

8 The aim of the second qualitative study will be to explore how information is presented within recruitment
9 appointments and how this might impact on consent to participate, with a view to ensuring robust trial
10 procedures using an iterative process. This will be achieved by audio-recording (with consent) up to 75
11 consultations between GPs or research assistants and eligible patients.
12
13

14 Thematic analysis will be undertaken on a sample of around 15-20 consultations comprising patients who
15 did, or did not consent to participate, to consider (a) terminology used, (b) presentation of the de-
16 prescribing approach and (c) presentation of randomisation. This will inform on-going trial procedures and
17 future implementation.
18
19

20 **Economic sub-study**

21 This work will adapt a previous decision-analytic model examining the long-term costs and benefits from
22 blood pressure lowering treatment³² to include potential harms of treatment. The model will be adjusted
23 for the effects of blood pressure lowering on cardiovascular disease risk, costs and quality-adjusted-life
24 years (QALYs) to match the older population involved in this work. Costs of the therapies prescribed, side-
25 effects and acute and long term costs of cardiovascular events will be obtained within the trial and from
26 the literature. Quality of life on each treatment strategy will be obtained from the trial data using EQ-5D-5L,
27 and previous studies will inform utility values for cardiovascular disease health states and the impact of
28 side effects. The model will determine the cost per additional QALY gained of the medication reduction
29 intervention versus usual care and analyses will be conducted from a health and social services perspective.
30 The model will be run with a lifetime perspective, with costs and benefits discounted at a rate of 3.5%. A
31 value of information analysis will assess whether a further trial would be appropriate to reduce decision
32 uncertainty, and identify those parameters where more precise estimates would be most valuable and
33 should therefore be chosen as outcomes for such a trial.
34
35
36
37
38

39 **Ethics and dissemination**

40 This research involves older participants, some of whom may be considered vulnerable. Great care will be
41 taken to ensure all potential participants have the trial clearly explained, and are given sufficient time to
42 decide whether to give informed consent. This will include provision of simplified, participant information
43 sheets with large fonts, video infographics to explain the study and extended GP consultation periods for
44 explaining the study and taking informed consent. The protocol, informed consent form, participant
45 information sheet and all other participant facing material have been approved by the Research Ethics
46 Committee (South Central - Oxford A; ref 16/SC/0628), Medicines and Healthcare products Regulatory
47 Agency (ref 21584/0371/001-0001), host institution(s) and Health Research Authority.
48
49
50

51 All research outputs from this work will be published in peer-reviewed journals, presented at scientific
52 conferences and lay and social media (e.g. Twitter, blogs). 'Patient friendly' study summary documents and
53 infographics will be made available to all participants at the end of the trial via the study website.
54
55
56
57
58
59

Discussion

Current guidelines in the UK suggest that doctors should ensure that patients are fully informed of the benefits and risks of their prescribed medications and where appropriate, discuss the potential for medication withdrawal in frail individuals with multi-morbidity.³³ This is difficult given consultation time constraints and fear that de-prescribing might result in harm.³⁴ This is compounded by conflicting and inconclusive evidence about the benefits and harms of treatment, and a lack of evidence about what will happen if these treatments are reduced.

The ECSTATIC trial enrolled 1,067 younger participants aged 40-70 years, taking antihypertensives for primary prevention of cardiovascular disease.¹⁸ The trial demonstrated that only 27% of participants were able to maintain medication reduction throughout follow-up and at 3 months, systolic blood pressure was on average 6 mmHg higher in the de-prescribing group. At 2 year follow-up, the risk of uncontrolled blood pressure was significantly higher in those patients attempting to de-prescribe. Unlike the present study, the medication reduction algorithm used did not encourage reintroduction of therapy if blood pressure was persistently raised.

The DANTE study¹⁶ 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 7/3 mmHg increase in blood pressure but no difference in overall cognition compound score or quality of life between groups. A study by Van der Wardt and colleagues¹⁹ examined the feasibility trial reducing antihypertensives in patients with dementia, but was only able to recruit 9 participants for the withdrawal programme (1% recruitment rate) and a larger trial was deemed unfeasible. Similarly, the OPTIMED trial³⁵ demonstrated in 95 participants that a broader de-prescribing approach is achievable in patients living in nursing homes, but was unable to examine the effect on clinical outcomes due to recruitment issues resulting on only 38% of the planned sample size being enrolled.

The OPTiMISE trial will target frail individuals with polypharmacy and co-morbidity, and aim to establish whether a strategy of antihypertensive medication reduction is safe and acceptable to older patients. The findings of this trial will support better patient-centred management plans for the prevention of cardiovascular disease in older individuals and inform future de-prescribing trials in primary care.

Acknowledgements

The authors acknowledge the support of the Primary Care Clinical Trials Unit, staff from the NIHR CRNs including Thames Valley and South Midlands, Cambridge, Southampton, West Midlands (Central and South) and West of England, and Lucy Curtin for administrative support. Margaret Ogden and Anita Higham serve as patient representatives for the trial steering committee. Additional members of the trial steering committee are Prof Tom Robinson (chair), Prof Rod Taylor and Dr Peter Bower. Members of the data monitoring committee are Prof John Gladman (chair), Prof Una Martin and Dr Martyn Lewis. The sponsor and funder had no role in the study design, writing of the paper; or the decision to submit this protocol for publication, which was made jointly by the authors who have all approved the final manuscript. Finally, this work would not be possible without the support of the participating practices and participants.

Funding

This work receives joint funding from the National Institute for Health Research (NIHR) Oxford Collaboration for Leadership in Applied Health Research and Care (CLAHRC) at Oxford Health NHS Foundation Trust (ref: P2-501) and the NIHR School for Primary Care Research (SPCR; ref 335). JS and RJMcM have been funded by an NIHR Professorship (NIHR-RP-R2-12-015). FDRH acknowledges part support from the NIHR SPCR, the NIHR CLAHRC Oxford, and the NIHR Oxford Biomedical Research Centre (BRC). CH receives support from the NIHR SPCR and NIHR Oxford BRC. The views and opinions expressed are those of the authors and do not necessarily reflect those of the NHS, NIHR, or the Department of Health.

Competing interests

The authors declare no conflicts of interest.

Author's contributions

JS conceived, designed and secured funding for the study with JBu, ML, JBe, GF, CH, FDRH, SJ, PL, JM, EO, RP, MW, LMY and RJMcM. JS wrote the first draft. AN and LMY provided the sample size calculations and statistical analysis section. JBu provided the qualitative section. SJ provided the health economic section. All authors reviewed and edited the manuscript. ET is the trial manager. JS and RJMcM are co-chief investigators and will act as guarantors for this work.

Data sharing

Data sharing requests will be considered by the corresponding author.

References

1. Office for National Statistics. Mid-year populations estimates: Aging, fastest increase in the 'oldest old'. <http://www.ons.gov.uk>, 2010.
2. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;380(9836):37-43. doi: 10.1016/s0140-6736(12)60240-2 [published Online First: 2012/05/15]
3. Violan C, Foguet-Boreu Q, Roso-Llorach A, et al. 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. doi: 10.1186/1471-2458-14-530 [published Online First: 2014/06/03]
4. Sheppard JP, Singh S, Fletcher K, et al. 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. doi: 10.1136/bmj.e4535 [published Online First: 2012/07/14]
5. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *The New England journal of medicine* 2008;358(18):1887-98. doi: 10.1056/NEJMoa0801369 [published Online First: 2008/04/02]
6. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *The New England journal of medicine* 2015 doi: 10.1056/NEJMoa1511939 [published Online First: 2015/11/10]
7. McKee M, Britton A, Black N, et al. Interpreting the evidence: choosing between randomised and non-randomised studies. *BMJ (Clinical research ed)* 1999;319(7205):312-5.
8. van Deudekom FJ, Postmus I, van der Ham DJ, et al. External validity of randomized controlled trials in older adults, a systematic review. *PloS one* 2017;12(3):e0174053. doi: 10.1371/journal.pone.0174053 [published Online First: 2017/03/28]
9. Bejan-Angoulvant T, Saadatian-Elahi M, Wright JM, et al. 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. doi: 10.1097/HJH.0b013e328339f9c5 [published Online First: 2010/06/25]
10. Benetos A, Labat C, Rossignol P, et al. Treatment With Multiple Blood Pressure Medications, Achieved Blood Pressure, and Mortality in Older Nursing Home Residents: The PARTAGE Study. *JAMA internal medicine* 2015 doi: 10.1001/jamainternmed.2014.8012 [published Online First: 2015/02/17]
11. Tinetti ME, Han L, Lee DS, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. *JAMA internal medicine* 2014;174(4):588-95. doi: 10.1001/jamainternmed.2013.14764 [published Online First: 2014/02/26]
12. Fried TR, Tinetti ME, Towle V, et al. 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. doi: 10.1001/archinternmed.2011.32 [published Online First: 2011/03/02]
13. Schuling J, Gebben H, Veehof LJ, et al. Deprescribing medication in very elderly patients with multimorbidity: the view of Dutch GPs. A qualitative study. *BMC family practice* 2012;13:56. doi: 10.1186/1471-2296-13-56 [published Online First: 2012/06/16]
14. Scott IA, Anderson K, Freeman CR, et al. First do no harm: a real need to deprescribe in older patients. *The Medical journal of Australia* 2014;201(7):390-2. [published Online First: 2014/10/09]

- 1
2 15. Iyer S, Naganathan V, McLachlan AJ, et al. Medication withdrawal trials in people aged 65 years and
3 older: a systematic review. *Drugs & aging* 2008;25(12):1021-31. doi: 10.2165/0002512-200825120-00004
4 [published Online First: 2008/11/22]
- 5
6 16. Moonen JE, Foster-Dingley JC, de Ruijter W, et al. Effect of Discontinuation of Antihypertensive
7 Treatment in Elderly People on Cognitive Functioning--the DANTE Study Leiden: A Randomized Clinical Trial.
8 *JAMA internal medicine* 2015;175(10):1622-30. doi: 10.1001/jamainternmed.2015.4103 [published Online
9 First: 2015/08/25]
- 10
11 17. van der Wardt V, Harrison JK, Welsh T, et al. Withdrawal of antihypertensive medication: a systematic
12 review. *Journal of hypertension* 2017;35(9):1742-49. doi: 10.1097/hjh.0000000000001405 [published
13 Online First: 2017/05/10]
- 14
15 18. Luymes CH, Poortvliet RKE, van Geloven N, et al. Deprescribing preventive cardiovascular medication in
16 patients with predicted low cardiovascular disease risk in general practice - the ECSTATIC study: a cluster
17 randomised non-inferiority trial. *BMC medicine* 2018;16(1):5. doi: 10.1186/s12916-017-0988-0 [published
18 Online First: 2018/01/13]
- 19
20 19. van der Wardt V, Burton JK, Conroy S, et al. Withdrawal of antihypertensive therapy in people with
21 dementia: feasibility study. *Pilot and feasibility studies* 2018;4:29. doi: 10.1186/s40814-017-0221-0
22 [published Online First: 2018/01/18]
- 23
24 20. Clegg A, Bates C, Young J, et al. Development and validation of an electronic frailty index using routine
25 primary care electronic health record data. *Age and ageing* 2016;45(3):353-60. doi: 10.1093/ageing/afw039
26 [published Online First: 2016/03/06]
- 27
28 21. National Clinical Guideline C. National Institute for Health and Clinical Excellence Guidance CG127.
29 Hypertension: The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18
30 and 34. London: Royal College of Physicians (UK) 2011.
- 31
32 22. Mattu GS, Heran BS, Wright JM. Overall accuracy of the BpTRU--an automated electronic blood
33 pressure device. *Blood pressure monitoring* 2004;9(1):47-52. [published Online First: 2004/03/17]
- 34
35 23. Lahrman H, Cortelli P, Hilz M, et al. EFNS guidelines on the diagnosis and management of orthostatic
36 hypotension. *European journal of neurology* 2006;13(9):930-6. doi: 10.1111/j.1468-1331.2006.01512.x
37 [published Online First: 2006/08/26]
- 38
39 24. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version
40 of EQ-5D (EQ-5D-5L). *Quality of life research : an international journal of quality of life aspects of treatment,*
41 *care and rehabilitation* 2011;20(10):1727-36. doi: 10.1007/s11136-011-9903-x [published Online First:
42 2011/04/12]
- 43
44 25. Gallagher P, Ryan C, Byrne S, et al. STOPP (Screening Tool of Older Person's Prescriptions) and START
45 (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *International journal of clinical*
46 *pharmacology and therapeutics* 2008;46(2):72-83. [published Online First: 2008/01/26]
- 47
48 26. McManus RJ, Mant J, Bray EP, et al. Telemonitoring and self-management in the control of
49 hypertension (TASMINH2): a randomised controlled trial. *Lancet* 2010;376(9736):163-72. doi:
50 10.1016/s0140-6736(10)60964-6 [published Online First: 2010/07/14]
- 51
52 27. McManus RJ, Mant J, Haque MS, et al. Effect of self-monitoring and medication self-titration on systolic
53 blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized
54 clinical trial. *Jama* 2014;312(8):799-808. doi: 10.1001/jama.2014.10057 [published Online First:
55 2014/08/27]
- 56
57
58
59
60

- 1
2 28. Cuspidi C, Meani S, Lonati L, et al. Prevalence of home blood pressure measurement among selected
3 hypertensive patients: results of a multicenter survey from six hospital outpatient hypertension clinics in
4 Italy. *Blood pressure* 2005;14(4):251-6. doi: 10.1080/08037050500210765 [published Online First:
5 2005/08/30]
- 6
7 29. Tucker KL, Sheppard JP, Stevens R, et al. Self-monitoring of blood pressure in hypertension: A
8 systematic review and individual patient data meta-analysis. *PLoS medicine* 2017;14(9):e1002389. doi:
9 10.1371/journal.pmed.1002389 [published Online First: 2017/09/20]
- 10
11 30. Walker E, Nowacki AS. Understanding equivalence and noninferiority testing. *Journal of general internal*
12 *medicine* 2011;26(2):192-6. doi: 10.1007/s11606-010-1513-8 [published Online First: 2010/09/22]
- 13
14 31. Nathan A, Goodyer L, Lovejoy A, et al. 'Brown bag' medication reviews as a means of optimizing
15 patients' use of medication and of identifying potential clinical problems. *Family practice* 1999;16(3):278-
16 82. [published Online First: 1999/08/10]
- 17
18 32. Kaambwa B, Bryan S, Jowett S, et al. Telemonitoring and self-management in the control of
19 hypertension (TASMINH2): a cost-effectiveness analysis. *European journal of preventive cardiology*
20 2014;21(12):1517-30. doi: 10.1177/2047487313501886 [published Online First: 2013/08/31]
- 21
22 33. National Guideline Centre. National Institute for Health and Care Excellence: Clinical Guidelines.
23 Multimorbidity: Assessment, Prioritisation and Management of Care for People with Commonly Occurring
24 Multimorbidity [NICE Guideline 56]. London: National Institute for Health and Care Excellence (UK)
25
- 26 Copyright (c) National Institute for Health and Care Excellence, 2016. 2016.
- 27
28 34. Palagyi A, Keay L, Harper J, et al. Barricades and brickwalls--a qualitative study exploring perceptions of
29 medication use and deprescribing in long-term care. *BMC geriatrics* 2016;16:15. doi: 10.1186/s12877-016-
30 0181-x [published Online First: 2016/01/16]
- 31
32 35. Potter K, Flicker L, Page A, et al. Deprescribing in Frail Older People: A Randomised Controlled Trial. *PloS*
33 *one* 2016;11(3):e0149984. doi: 10.1371/journal.pone.0149984 [published Online First: 2016/03/05]
- 34
35 36. Sulter G, Steen C, De Keyser J. Use of the Barthel index and modified Rankin scale in acute stroke trials.
36 *Stroke; a journal of cerebral circulation* 1999;30(8):1538-41. [published Online First: 1999/08/06]
- 37
38 37. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle
39 aged African Americans. *The journal of nutrition, health & aging* 2012;16(7):601-8. [published Online First:
40 2012/07/28]
- 41
42 38. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people.
43 *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*
44 2005;173(5):489-95. doi: 10.1503/cmaj.050051 [published Online First: 2005/09/01]
- 45
46 39. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief
47 screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society* 2005;53(4):695-9.
48 doi: 10.1111/j.1532-5415.2005.53221.x [published Online First: 2005/04/09]
- 49
50 40. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to
51 treatment in chronic physical illness. *Journal of psychosomatic research* 1999;47(6):555-67. [published
52 Online First: 2000/02/08]
- 53
54
55
56
57
58
59

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Tables

Table 1. Trial inclusion and exclusion criteria

| Inclusion criteria |
|--|
| <ul style="list-style-type: none"> Participant is willing and able to give informed consent for participation in the trial. |
| <ul style="list-style-type: none"> Male or Female, aged 80 years or above. |
| <ul style="list-style-type: none"> 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). |
| <ul style="list-style-type: none"> 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, beta-blocker, vasodilator antihypertensives, centrally acting antihypertensives, direct renin inhibitors, adrenergic neurone blocking drugs or loop diuretics. |
| <ul style="list-style-type: none"> Stable dose of antihypertensive medications for at least four weeks prior to trial entry. |
| <ul style="list-style-type: none"> 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 |
| <ul style="list-style-type: none"> In the Investigator's opinion, is able and willing to comply with all trial requirements. |
| Exclusion criteria |
| <ul style="list-style-type: none"> A participant has heart failure due to LVSD and is on only ACE inhibitors/ARBs and/or beta-blockers and/or spironolactone (removing any of which would be contraindicated). |
| <ul style="list-style-type: none"> A participant has heart failure but has not had an echocardiogram since its onset (might have undiagnosed LVSD and a compelling need for ACE inhibitors/ARB and Beta-blockers). |
| <ul style="list-style-type: none"> Investigator deems that there is a compelling indication for antihypertensive medication continuation. |
| <ul style="list-style-type: none"> 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). |
| <ul style="list-style-type: none"> Suffered a myocardial infarction or stroke within the past 12 months. |
| <ul style="list-style-type: none"> Blood pressure being managed outside of primary care. |
| <ul style="list-style-type: none"> Unable to provide consent due to incapacity. |
| <ul style="list-style-type: none"> A participant with secondary hypertension or previous accelerated or malignant hypertension. |
| <ul style="list-style-type: none"> Participants who have participated in another research trial involving antihypertensive medication in the past 4 weeks. |

LVSD=Left ventricular systolic dysfunction; ACE inhibitor=Angiotensin Converting Enzyme inhibitor;
ARB=Angiotensin II receptor blocker

Table 2. Variables and schedule of data collection

| No. | Variable | Data source | | Schedule | |
|-----|---|---------------|------------------------------|----------|-----------|
| | | Medical notes | Measured/collected at clinic | Baseline | 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) ²⁴ | | ✓ | ✓ | ✓ |
| 17 | Functional independence (defined by modified Rankin Scale) ³⁶ | | ✓ | ✓ | |
| 18 | Frailty (according to the FRAIL scale) ³⁷ | | ✓ | ✓ | ✓ |
| 19 | Frailty (according to the frailty index and electronic frailty index) ^{20 38} | ✓ | ✓ | ✓ | ✓ |
| 20 | Cognitive function (defined by the Montreal Cognitive Assessment [MoCA]) ³⁹ | | ✓ | ✓ | |
| 21 | Adherence to medication (according to the Medication Adherence Rating Scale (MARS) Questionnaire) ⁴⁰ | | ✓ | ✓ | ✓ |
| 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)

Figure legends

Figure 1. Trial flow diagram

*Monitoring of blood pressure at home will be encouraged but those not willing or able will still be included in the trial. All participants 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

Figure 2. Medication reduction algorithm

STOPP criteria²⁵

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).

Figure 3. Post medication reduction monitoring flow chart

Note: 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 above). 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.²¹

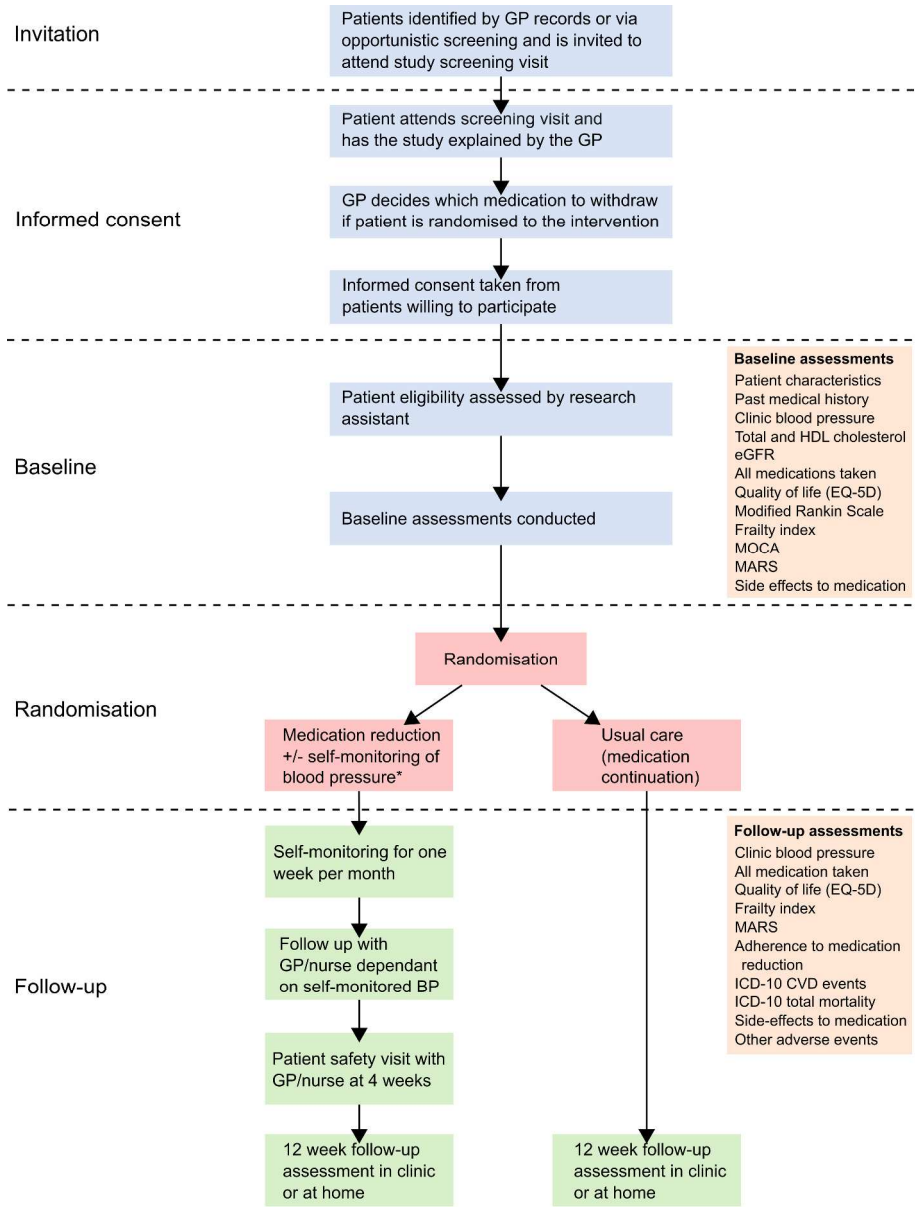


Figure 1

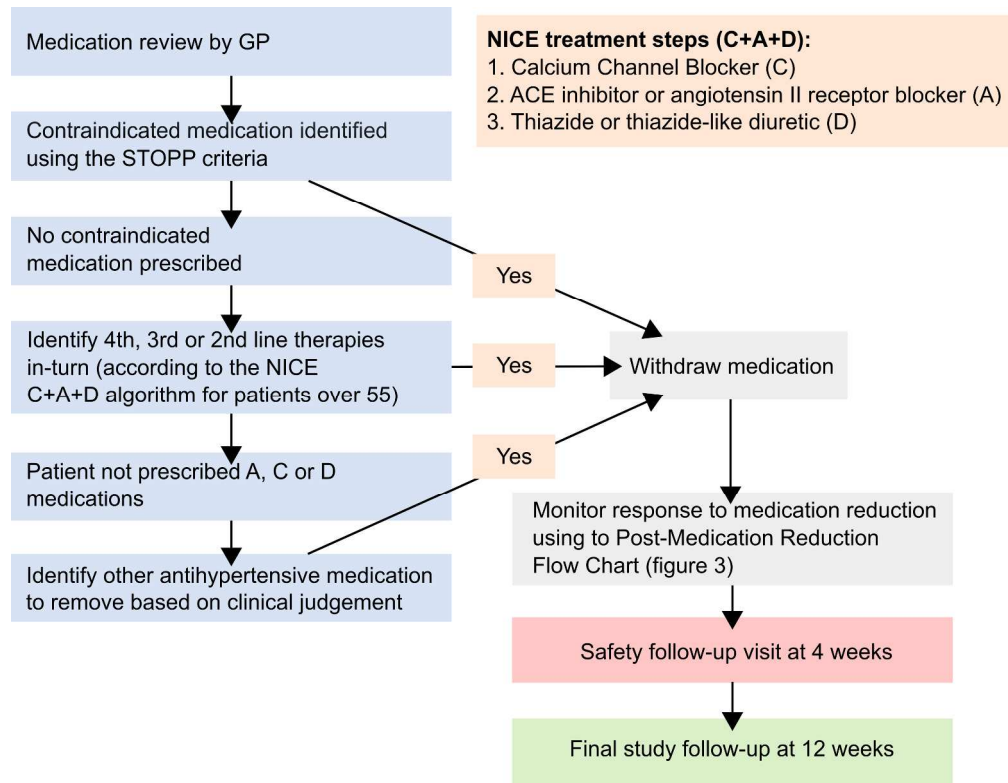


Figure 2

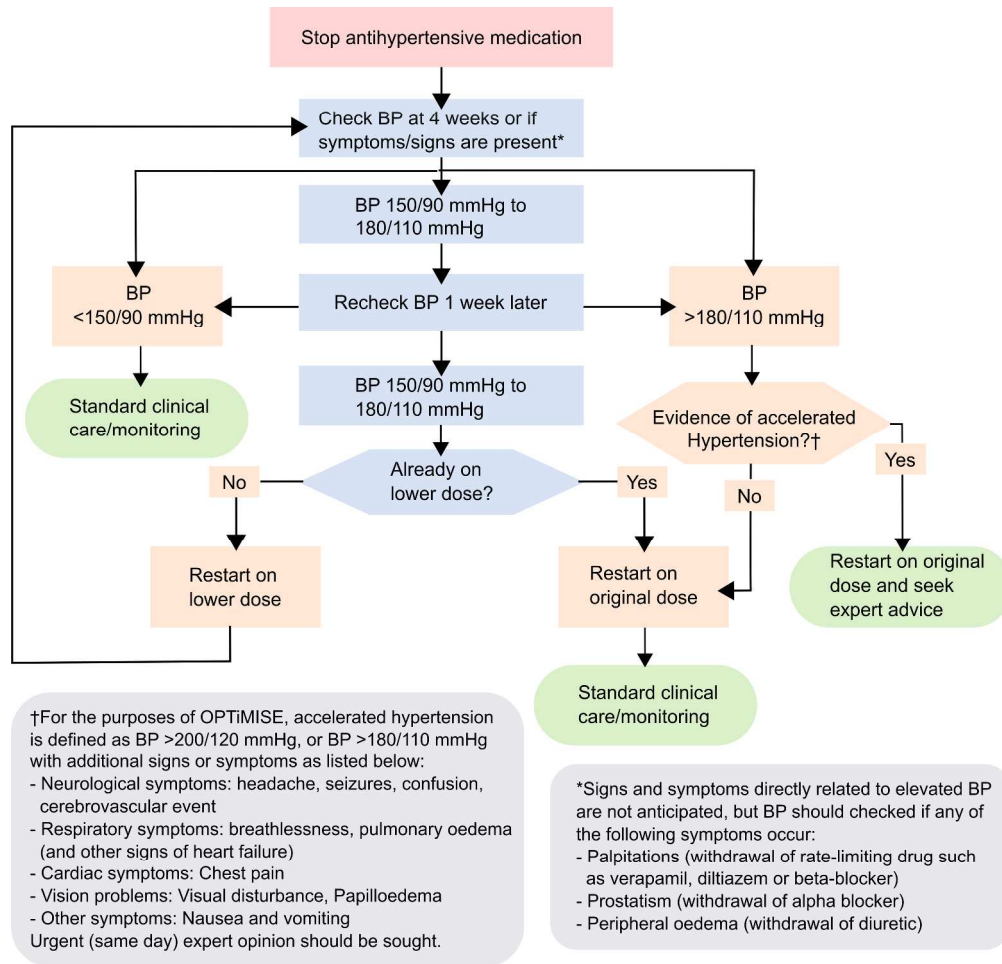


Figure 3



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Page in protocol |
|---|---------|--|------------------|
| Administrative information | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | n/a |
| Protocol version | 3 | Date and version identifier | n/a |
| Funding | 4 | Sources and types of financial, material, and other support | 12 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1, 12 |
| | 5b | Name and contact information for the trial sponsor | 1 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 12 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 12 |
| Introduction | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 3 |
| | 6b | Explanation for choice of comparators | 3 |
| Objectives | 7 | Specific objectives or hypotheses | 3-4 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 4 |
| Methods: Participants, interventions, and outcomes | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 4 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will | 4, table 1 |

| | | | |
|---|-----|--|----------|
| | | perform the interventions (eg, surgeons, psychotherapists) | |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 5 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | Figure 3 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 6-7 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 7 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 4-5 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Figure 1 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 8 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 5 |
| Methods: Assignment of interventions (for controlled trials) | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 6 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 6 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 6 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 6 |

| | | | |
|---|-----|--|-----|
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 6 |
| Methods: Data collection, management, and analysis | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 5-7 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 7 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 6 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 8 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 8 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 8 |
| Methods: Monitoring | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 9 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 9 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 9 |
| Ethics and dissemination | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 10 |

| | | | |
|-------------------------------|-----|---|-----|
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | n/a |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 5 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | n/a |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 12 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 12 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | n/a |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 10 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | n/a |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | n/a |
| Appendices | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | n/a |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

OPTimising Treatment for MIld Systolic hypertension in the Elderly (OPTiMISE): protocol for a randomised controlled non-inferiority trial

| | |
|---------------------------------|--|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2018-022930.R1 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 14-Jun-2018 |
| Complete List of Authors: | Sheppard, James; University of Oxford, Nuffield Department of Primary Care Health Sciences Burt, Jenni; University of Cambridge, Cambridge Centre for Health Services Research Lown, Mark; University of Southampton Temple, Eleanor; University of Oxford, Nuffield Department of Primary Care Health Sciences Benson, John; University of Cambridge, GP and Primary Care Research Unit Ford, Gary; Oxford University Hospitals NHS Foundation Trust, Oxford Academic Health Science Network Heneghan, Carl; Oxford University, Primary Health Care Hobbs, Richard; University of Oxford, Nuffield Department of Primary Care Health Sciences Jowett, Sue; University of Birmingham, Health Economics Unit Little, Paul; University of Southampton, Primary Care and Population Science; Mant, Jonathan; University of Cambridge, General Practice and Primary Care Research Unit Mollison, Jill; University of Oxford, Nuffield Department of Primary Care Health Sciences Nickless, Alecia; University of Oxford, Nuffield Department of Primary Care Health Sciences Ogburn, Emma; University of Oxford, Payne, Rupert; University of Bristol, Centre for Academic Primary Care Williams, Marney; Patient and public involvement representative Yu, Ly-Mee; University of Oxford, Department of Primary Care Health Sciences McManus, Richard; University of Oxford, Dept of Primary Care Health Sciences |
| Primary Subject Heading: | General practice / Family practice |
| Secondary Subject Heading: | Cardiovascular medicine, Geriatric medicine, Health services research |
| Keywords: | Multi-morbidity, Cardiovascular disease, Frailty, Antihypertensive, De-prescribing |
| | |

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.

OPTIMISE video infographic V1.1 14.03.17.mp4

SCHOLARONE™
Manuscripts

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **Optimising Treatment for Mild Systolic hypertension in the Elderly (OPTiMISE): protocol for a randomised**
2 **controlled non-inferiority trial**

3
4 James P Sheppard,¹ Jenni Burt,² Mark Lown,³ Eleanor Temple,¹ John Benson,⁴ Gary A Ford,¹ Carl Heneghan,¹
5 FD Richard Hobbs,¹ Sue Jowett,⁵ Paul Little,³ Jonathan Mant,⁴ Jill Mollison,¹ Alecia Nickless,¹ Emma Ogburn,¹
6 Rupert Payne,⁶ Marney Williams,⁷ Ly-Mee Yu,¹ and Richard J McManus¹

7
8 ¹Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

9 ²The Healthcare Improvement Studies Institute, University of Cambridge, Cambridge, UK

10 ³Primary Care Research Group, University of Southampton, Southampton, UK

11 ⁴Primary Care Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

12 ⁵Institute of Applied Health Research, University of Birmingham, Birmingham, UK

13 ⁶Centre for Academic Primary Care, University of Bristol, Bristol, UK

14 ⁷Patient and public involvement representative, London, UK

15
16 **Corresponding author:** James P Sheppard

17 **Email:** james.sheppard@phc.ox.ac.uk

18 **Telephone:** +44 1865 617192

19 **Address:** Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care Building, Radcliffe
20 Observatory Quarter, University of Oxford, Oxford, OX2 6GG, UK

21
22 **Trial Sponsor:** University of Oxford

23 **Contact name:** Ms Heather House

24 **Address:** Clinical Trials and Research Governance, Joint Research Office, Block 60, Churchill Hospital,
25 University of Oxford, Oxford, OX3 7LE

26 **Email:** ctrg@admin.ox.ac.uk

27
28 **Word count:** 4,208 (excluding title page, abstract, references, tables and figures)

29 **Number of tables:** 2

30 **Number of figures:** 3

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59

Abstract

Introduction: Recent evidence suggests that larger blood pressure reductions and multiple antihypertensive drugs may be harmful in older people, particularly frail individuals with polypharmacy and multi-morbidity. However, there is a lack of evidence to support de-prescribing of antihypertensives, which limits the practice of medication reduction in routine clinical care. The aim of this trial is to examine whether antihypertensive medication reduction is possible in older patients without significant changes in blood pressure control at follow-up.

Methods and analysis: This trial will use a Primary Care based, open label, randomised controlled trial design. A total of 540 participants will be recruited, aged ≥ 80 years, with systolic blood pressure < 150 mmHg and receiving ≥ 2 antihypertensive medications. Participants will have no compelling indication for medication continuation and will be considered to potentially benefit from medication reduction due to existing polypharmacy, co-morbidity and frailty. Following a baseline appointment, individuals will be randomised to a strategy of medication reduction (intervention) with optional self-monitoring or usual care (control). Those in the intervention group will have one antihypertensive medication stopped. The primary outcome will be to determine if a reduction in medication can achieve a proportion of participants with clinically safe blood pressure levels at 12 week follow-up (defined as a systolic blood pressure < 150 mmHg) which is non-inferior (within 10%) to that achieved by the usual care group. Qualitative interviews will be used to understand the barriers and facilitators to medication reduction. The study will use economic modelling to predict the long term effects of any observed changes in blood pressure and quality-of-life.

Ethics and dissemination: The protocol and written information has been approved by a Research Ethics Committee, medicines regulatory authority (MHRA), and national and local health research authorities. All research outputs will be published in peer-reviewed journals and presented at national and international conferences.

Trial registration: EudraCT 2016-004236-38

Word count: 299 (max 300)

Keywords: Multi-morbidity, cardiovascular disease, frailty, antihypertensive, de-prescribing

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

60 **Strengths and limitations of this study**

- 61 • This will be the first UK randomised controlled trial to compare a strategy of antihypertensive
62 medication reduction to usual care in primary care.
- 63 • The pragmatic trial design, with broad inclusion criteria, will make findings of the study externally valid
64 in routine clinical practice.
- 65 • Allowing the attending GP to choose the medication to be reduced will maximise external validity of
66 the trial results but precludes the possibility of blinding the participants and investigators.
- 67 • The trial will be powered to detect a non-inferior difference in blood pressure control at follow-up, but
68 not necessarily secondary outcomes such as differences in rates of cardiovascular disease, adverse
69 events and quality of life.

For peer review only

70 Introduction

71 The general population is ageing¹ and, consequently, the number of people living with age-related chronic
72 conditions is increasing.² Hypertension is the number one co-morbid condition in older people with
73 multiple chronic conditions³ and 52% of those aged ≥ 80 years are prescribed two or more antihypertensive
74 drugs (equivalent to approximately 1.25 million people in the UK).⁴ Blood pressure lowering has been
75 shown to be effective at preventing stroke and cardiovascular disease in healthy individuals aged ≥ 80 years
76 with stage 2 hypertension (systolic blood pressure of >160 mmHg) and high risk stage 1 hypertension.^{5,6}
77 However, as with many trials,^{7,8} these studies included healthier populations with lower polypharmacy and
78 multi-morbidity than might be expected in the general elderly population. In addition, there is evidence to
79 suggest that larger blood pressure reductions and multiple antihypertensive prescriptions may be harmful
80 in older people.^{9,10} Evidence from observational studies also suggests that higher intensity blood pressure
81 treatment is associated with increased risk of falls in older people,¹¹ although this is also disputed.⁵

82
83 Some patients consider the increased risk of falls and other adverse events to be as important as the risk of
84 myocardial infarction or stroke, particularly those taking medications for primary prevention of
85 cardiovascular disease.¹² Thus, decisions over blood pressure lowering in the elderly, particularly the frail
86 elderly, require the weighing of harms and quality of life. However, clinicians can often struggle to stop
87 prescribing medication due to a perceived lack of evidence, fear of the reaction of other prescribers, fear of
88 precipitating events such as stroke or angina and concern that patients will feel their care is being cut.^{13,14}

89
90 There is limited evidence from randomised trials examining the safety of antihypertensive medication
91 reduction or withdrawal.¹⁵⁻¹⁹ The HYVET trial⁵ enrolled some patients on antihypertensive treatment who
92 were then randomised to placebo (effectively complete medication withdrawal) and the ANBP2 trial
93 investigators followed up participants who withdrew medication during the trial run-in period but who
94 were not randomised into the trial. They found younger patients with lower baseline blood pressure and
95 fewer drug prescriptions were more likely to sustain medication withdrawal at 12 month follow-up.^{20,21}
96 However, there are few trials comparing a specified strategy of antihypertensive medication reduction with
97 usual care in terms of effects on blood pressure control and quality of life.¹⁷ In addition, there are no
98 previous economic modelling studies of a strategy of medication reduction in the elderly.

99
100 The aim of this work will be to examine whether antihypertensive medication reduction in patients with
101 controlled systolic hypertension (≤ 150 mmHg) who are being prescribed two or more antihypertensives is
102 possible without significant changes in blood pressure control at follow-up.

104 Methods

105 *Aims and outcomes*

106 The aim of this study is to determine whether antihypertensive medications can be safely reduced without
107 systolic blood pressure increasing beyond what is clinical acceptable at follow-up.

108 The primary outcome is the proportion of participants with clinically acceptable levels at 12 week follow-up
109 (defined as a systolic blood pressure <150 mmHg) Secondary outcomes will examine:

- 110 • The proportion of participants in the intervention arm who maintain medication reduction through
111 to follow-up (*i.e.* are *not* restarted on therapy).
- 112 • The difference in quality of life (according to EQ-5D-5L) between groups at 12 week follow-up.
- 113 • The difference in frailty (according to the frailty index)²² between the two groups at 12 week follow-
114 up.

- 115 • The difference in the change in mean clinic systolic blood pressure (from baseline) between the two
- 116 groups at 12 week follow-up.
- 117 • The difference in reported side effects to medication between the two groups at 12 week follow-up
- 118 (including coughs, dizziness, syncope, and ankle swelling).
- 119 • The difference in routinely reported serious adverse events between the two groups at 12 week
- 120 follow-up (hospitalisation due to falls, myocardial infarction, stroke or all-cause mortality).

121

122 *Design*

123 This trial will use a Primary Care based, open label, randomised controlled, two-parallel groups, non-

124 inferiority trial design, recruiting 540 participants with controlled blood pressure (systolic <150 mmHg) on

125 two or more antihypertensive treatments. Participants will be randomised to a strategy of medication

126 reduction (intervention) or usual care (control) and followed-up for 12 weeks (see figure 1). Embedded

127 qualitative and economic analyses will examine barriers and facilitators to medication reduction and the

128 cost effectiveness of the approach.

129

130 *Trial participants*

131 Patients eligible for the trial will be aged ≥ 80 years, with systolic blood pressure <150mmHg (current UK

132 guideline recommendation)²³ receiving ≥ 2 antihypertensive medications. They will have no compelling

133 indication for medication continuation and in the opinion of the attending GP, may potentially benefit from

134 medication reduction due to existing polypharmacy, co-morbidity and/or frailty (table 1).

135

136 Participants will be identified and recruited from general practices via the UK Clinical Research Network

137 (CRN). Potentially eligible patients will be identified by trained practice staff searching practice-based

138 electronic disease registers using a standardised strategy. GPs will be asked to check the search results and

139 remove people whom they believe to be unsuitable to participate in the study. Remaining potentially

140 eligible patients will be sent letters of invitation from their GP and those expressing an interest in the trial

141 will be asked to attend a screening and baseline appointment. Patients not responding to the first invitation

142 will receive one reminder letter (up to four weeks after the first letter). Other potentially eligible patients

143 may also be approached opportunistically by a member of the clinical care team. Those who do not wish to

144 take part will be asked to fill in a short questionnaire detailing their reasons.

145

146 *Baseline visit*

147 Eligible patients will have informed consent taken by the GP. During the consent appointment, the GP will

148 show a two-minute study video infographic (see supplementary material) and go through the participant

149 information sheet explaining the exact nature of the trial. Having had a chance to ask questions, those

150 individuals willing to participate will give written informed consent by means of a participant dated

151 signature and dated signature of the GP who presented and obtained the informed consent.

152

153 Some participants will be invited to have their interview audio-recorded for qualitative analysis during their

154 study visits. Those who are interested will be asked to sign a response slip prior to meeting the GP. Consent

155 to audio recordings will not have a bearing on an individual's care or eligibility for the main trial.

156

157 Those giving informed consent will be screened using the criteria in table 1 and undergo baseline

158 measurements and randomisation by a member of the research team via participant questionnaires and a

159 detailed notes review (table 2). Blood pressure will be measured in a standardised fashion using the

160 clinically validated²⁴ BpTRU blood pressure monitor which automatically records six blood pressure

1 161 measurements at one minute intervals. Blood pressure readings will be taken in the left arm (where
2 162 appropriate) after participants have been seated for at least five minutes of rest, using an appropriate sized
3 163 cuff. The mean of the 2nd and 3rd readings will be used to define the primary outcome. To test for
4 164 orthostatic hypotension, two further readings will be taken in the standing position after one and three
5 165 minutes.²⁵ Only the research facilitator/nurse will be present during the blood pressure measurements.
6 166 Orthostatic hypotension will be defined as a ≥ 20 mmHg drop in systolic blood pressure within three minutes
7 167 of standing.
8 168

9 169 All data will be collected via an electronic case report form (eCRF) linked to the study database. Participants
10 170 will be given the option to enter responses to questionnaires themselves or with assistance from the
11 171 research team. Where questionnaires are not validated for use on a tablet computer,²⁶ or where individuals
12 172 are not comfortable using one, paper copies will be made available for completion.
13 173

14 174 *Randomisation*

15 175 Consenting participants will be individually randomised (1:1 allocation ratio) to one of two study arms using
16 176 a fully validated web-based system (Sortition[®]) with manual telephone back up. Participants will not be
17 177 randomised until after consent has been taken and baseline assessments have been completed. A
18 178 computer generated non-deterministic algorithm, minimising on practice and baseline systolic blood
19 179 pressure will be used to ensure these covariates are balanced between the two intervention arms.
20 180

21 181 The study will use an open label design, so patients and practitioners will not be blinded to the intervention
22 182 or study endpoints. Therefore, codebreaking will not be necessary. The statistical analysis will be
23 183 performed blind to patient allocation.
24 184

25 185 *Intervention group*

26 186 Participating GPs will review each participant's antihypertensive medication regimen prior to the baseline
27 187 appointment, and decide which medication should be removed if they are randomised to the intervention
28 188 arm of the trial. The choice of medication to be withdrawn will be at the discretion of the GP, but their
29 189 decision will be informed by an individual's co-morbidities and existing guidelines, where appropriate
30 190 (figure 2). Specifically, participating GPs will be encouraged to identify previously unrecognised
31 191 contraindications to medication, defined by the STOPP criteria.²⁷ In the absence of these, or a strong clinical
32 192 rationale for continuing despite a STOPP criteria being met, GPs will be recommended to reduce
33 193 antihypertensive medications in reverse of the NICE C+A+D algorithm for older patients (figure 2).²³ All
34 194 participants in the trial will remain on at least one antihypertensive.
35 195

36 196 Once a medication has been removed, GPs or other appropriate, delegated healthcare professionals will
37 197 closely monitor the participant's response to medication reduction: they will be given advice about what
38 198 and when to monitor (figure 3), but this schedule will be flexible. All participants will be expected to return
39 199 for at least one routine safety follow-up visit, and further visits may be required if blood pressure is raised
40 200 (≥ 150 mmHg), or adverse events occur. Where blood pressure is persistently raised, GPs will be expected to
41 201 re-adjust medication (dose or type), rendering the likelihood of a serious adverse event occurring as a
42 202 result of the intervention very low.
43 203

44 204 *Self-monitoring*

45 205 All participants randomised to the medication reduction arm of the trial will be given the option to self-
46 206 monitor their blood pressure at home. Those accepting will be trained using protocols developed in the
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2 207 previous TASMIN trials^{28 29} and will be given simple and clear instructions to contact their GP if their blood
3 208 pressure rises above what is considered clinically safe (e.g. home systolic blood pressure >145mmHg on all
4 209 readings taken in a week). Participants will be advised to self-monitor (or have a carer monitor) at least 4
5 210 times per week in the last week of each month of follow-up (weeks 4, 8 and 12), although they can monitor
6 211 more frequently if they wish. Differential use of self-monitoring in the intervention group, or indeed in the
7 212 control group (many patients now self-monitor routinely)³⁰ is not expected to impact on the study results,
8 213 since there is good evidence that self-monitoring only affects blood pressure levels if used in combination
9 214 with a co-intervention.³¹ All other clinical care will continue as usual.

11 215 12 216 *Control group*

13 217 Those allocated to the control arm of the study will continue usual clinical care (i.e. they will continue to
14 218 take antihypertensive medications as prescribed and will not self-monitor unless already doing so). No
15 219 other medication changes will be mandated and participating GPs will be asked to manage all other care
16 220 according to usual clinical practice.

17 221 18 222 *Follow-up visits*

19 223 Participants will attend one research follow-up clinic, 12 weeks (± 2 weeks) after baseline and those in the
20 224 intervention will attend one additional safety visit after four weeks (± 2 weeks) (figure 1). A period of four
21 225 weeks is expected to be sufficiently long enough to assess the impact of antihypertensive medication
22 226 reduction, since these drugs usually take approximately four weeks to 'wash out' of a patient's system.
23 227 Earlier safety visits are not recommended since they could provide false reassurance that blood pressure is
24 228 within safe limits if the withdrawn drug has not washed out of the participant's system.

25 229
26 230 The follow-up assessments will include standardised blood pressure measurement (for assessment of the
27 231 primary outcome), questionnaire assessments and adherence to the trial medication regime, side effects
28 232 and adverse events (table 2). Where possible, all participants will be flagged for mortality and hospital
29 233 admissions using NHS patient tracking services, permitting long-term follow-up for up to 5 years after the
30 234 trial has finished.

31 235
32 236 Each participant has the right to withdraw from the trial at any time. We will ask all participants to attend a
33 237 follow-up visit as far as is practicable, regardless of whether medication is re-introduced to participants in
34 238 the intervention group, or a participant in the control group has medication withdrawn. Unless a
35 239 participant withdraws consent, vital status will be assessed even where an individual has been lost to
36 240 follow-up (for instance moved away). If given, the reason for withdrawal will be recorded in the eCRF.

37 241 38 242 *Internal feasibility study*

39 243 A two-stage internal feasibility study will be conducted to examine methods of patient invitation and rates
40 244 of recruitment, before proceeding with the main trial. The first feasibility phase will last for a minimum of
41 245 three months and aim to recruit approximately 25 participants from a minimum of 3-5 practices. The aim
42 246 will be to establish whether or not anyone will be willing to participate in the study.

43 247
44 248 The second feasibility phase will focus on recruitment rates for the main trial and whether the intended
45 249 sample size is likely to be met during the recruitment period. This phase will have a recruitment target of 75
46 250 participants from ten practices over 6 months, giving a total sample for the feasibility study of 100
47 251 participants. A recruitment rate of 15% of invitations sent is expected. The following actions will be
48 252 considered to address varying rates of recruitment at the end of the feasibility phases:

- 1
2 253 - If ≥ 100 participants are recruited – trial will proceed as planned
3 254 - If 75-99 participants are recruited – recruitment materials/method will be re-examined and edited
4 255 where necessary following discussions with stakeholders and patient and public involvement
5 256 representatives.
6 257 - If 50-74 participants are recruited – the allocation of resources and recruitment criteria will be re-
7 258 examined using information gathered from concurrent qualitative work.
8 259 - If < 50 participants are recruited – the Trial Steering Committee (TSC) will decide, in discussion with
9 260 the Data Monitoring and Ethics Committee (DMEC) and the funders, whether the trial should be
10 261 stopped due to futility.
11 262

12 262 13 263 *Sample size calculation*

14 264 Assuming that 100% of participants in the usual care group, and 96% of those in the medication reduction
15 265 group have controlled systolic blood pressure levels (< 150 mmHg) at follow-up, approximately 540
16 266 participants will be required to detect a non-inferior difference in systolic blood pressure control between
17 267 groups. Calculations assume a 10% non-inferiority margin, 90% power, 2.5% 1-sided level of significance,
18 268 10% loss to follow-up and a 10% dilution effect due to cross-over between arms. There is no existing
19 269 precedent for an appropriate margin of non-inferiority in this type of trial, but 10% was deemed useful to
20 270 inform future doctor-patient discussions about medication reduction: if the non-inferiority margin is met, it
21 271 will suggest that for every ten patients who have their medication reduced, at least nine will still have
22 272 controlled blood pressure at 12 week follow-up.
23 273

24 274 *Statistical analysis*

25 275 A detailed statistical analysis plan will be agreed prior to the end of the trial. The primary and secondary
26 276 analyses will be by intention to treat (ITT), unless stated otherwise. The primary analysis will be a non-
27 277 inferiority analysis by means of the “two one-sided test” (TOST) procedure,³² whereby the 95% confidence
28 278 interval for the relative risk of participants with systolic blood pressure at 12 weeks below 150 mmHg
29 279 between the medication reduction group and the usual care group is calculated. This will be obtained by
30 280 means of a generalised linear mixed effects model with GP surgery included as a random effect and
31 281 baseline blood pressure as a fixed effect. If the lower limit of the confidence interval is more than 0.9 (equal
32 282 to a risk difference of 10%) then the research hypothesis that medication reduction will be non-inferior in
33 283 terms of blood pressure control to usual care will be accepted. As a secondary analysis of the primary
34 284 outcome, a per-protocol (PP) analysis will be performed, since ITT can be anticonservative for a non-
35 285 inferiority hypothesis.³² Participants who received the medication reduction intervention in the PP analysis
36 286 will be defined as a participant in the medication reduction arm who maintained their medication reduction
37 287 throughout the 12 week follow-up period.
38 288

39 289 Secondary analyses will examine the proportion of participants in the medication reduction arm who
40 290 maintained their medication reduction throughout the 12 week follow-up period. Secondary outcomes will
41 291 be analysed by means of linear mixed effects models, adjusting for the baseline level of the outcome and
42 292 baseline systolic blood pressure and including practice as a random effect: systolic blood pressure, EQ-5D-
43 293 5L and the Frailty index/frail scale. The difference in the rate of side effects and adverse events between
44 294 the medication reduction and usual care arms will be analysed by means of a logistic mixed effects model
45 295 adjusting for baseline systolic blood pressure and including practice as a random effect.
46 296

1
2 297 Exploratory subgroup analyses of blood pressure control, change in blood pressure and maintenance of
3 298 medication reduction will be conducted by different levels of baseline frailty, functional independence,
4 299 cognitive function, number of medications prescribed at baseline and number of co-morbidities at baseline.
5 300

6 301 **Patient and public involvement**

7 302 This protocol was developed through discussions with older patients and carers and members of an AgeUK
8 303 day centre. MW is a stroke survivor with experience as a volunteer on the elderly ward of Charing Cross
9 304 Hospital. She was consulted on the suitability and design of the trial and is a member of the trial
10 305 management group. Methods of patient approach, including the design of the video infographic, patient
11 306 information sheet and consent form were all reviewed by patient representatives prior to formal approval.
12 307 The TSC includes two independent patient representatives responsible for overseeing the conduct of the
13 308 trial.
14 309

15 310 **Safety reporting**

16 311 Adverse events that are observed by an investigator or reported by the participant will be recorded on the
17 312 AE log at any time during the study but AEs will be specifically asked about at the 12 week follow up.
18 313 Serious adverse events (SAEs) will be reported to the coordinating centre within 24 hours of discovery or
19 314 notification of the event. All SAE reports will be reviewed by the DMEC chair on a monthly basis, and by the
20 315 full DMEC at meetings held every 6 months. The DMEC will include a geriatrician, statistician and consultant
21 316 clinical pharmacologist. They will be responsible for safeguarding trial participants, monitoring emerging
22 317 trial data including identifying any trends, such as increases in unexpected events, and take appropriate
23 318 action where necessary.
24 319

25 320 All adverse events labelled possibly, probably or definitely related will be considered as related to the
26 321 intervention. Since there are no sections of the Summary of medicinal Product Characteristics, or previous
27 322 clinical studies which detail expected adverse events as a result of medication withdrawal, all SAEs at least
28 323 possibly related, and not as a result of re-introduction of withdrawn medication, will be considered
29 324 unexpected and reported as SUSARs. Fatal and life-threatening SUSARs will be reported by the chief
30 325 investigator to the relevant Competent Authority and Research Ethics Committee no later than 7 calendar
31 326 days after the Sponsor or delegate is first aware of the reaction. All other SUSARs will be reported within 15
32 327 calendar days.
33 328

34 329 **Qualitative sub-studies**

35 330 *Study 1: interviews with doctors and patient*

36 331 Face-to-face interviews with GPs and patients will be conducted to generate understanding about the
37 332 barriers and facilitators to antihypertensive medication reduction. Informed consent will be sought from
38 333 approximately 15 GPs to provide a broad range of opinion from varying practice sizes (small to large) and
39 334 settings (rural to urban). Participating GPs will also be asked to identify up to 15 patients for interview,
40 335 based on the same inclusion criteria as those applied to participants in the main trial.
41 336

42 337 Interviews with GPs will use a chart-stimulated recall approach to explore the factors which influence their
43 338 treatment choices in older hypertensive patients. Anonymised electronic health records will be used to
44 339 focus discussions about how GPs would feel about reducing antihypertensive medications. Interviews with
45 340 patients will use 'brown bag' medication review techniques³³ to create a complete record of medication
46 341 held, with a commentary on usage from the participants' perspective. Diagrammatic elicitation techniques
47 342 will be used to complete a relational map outlining participants' circumstances and how these relate to the
48 343

1 343 medications taken. These sketches will be used as the basis for a discussion on the implications of
2 344 withdrawing antihypertensive medications, and what this “gap” might mean for the patient.

3 345
4 346 All interviews will be transcribed verbatim, stored and organised using NVivo software (QSR International
5 347 Pty Ltd, Doncaster, Victoria, Australia). Interview and visual data from GP and patient interviews will be
6 348 subjected to thematic analysis, with a particular orientation to exploring clinical and patient perspectives
7 349 on the barriers and facilitators to reducing antihypertensives.

8 350

9 351 *Study 2: Assessment of trial recruitment and data collection procedures*

10 352 The aim of the second qualitative study will be to explore how information is presented within recruitment
11 353 appointments and how this might impact on consent to participate, with a view to ensuring robust trial
12 354 procedures using an iterative process. This will be achieved by audio-recording (with consent) up to 75
13 355 consultations between GPs or research assistants and eligible patients.

14 356

15 357 Thematic analysis will be undertaken on a sample of around 15-20 consultations comprising patients who
16 358 did, or did not consent to participate, to consider (a) terminology used, (b) presentation of the de-
17 359 prescribing approach and (c) presentation of randomisation. This will inform on-going trial procedures and
18 360 future implementation.

19 361

20 362 **Economic sub-study**

21 363 This work will adapt a previous decision-analytic model examining the long-term costs and benefits from
22 364 blood pressure lowering treatment³⁴ to include potential harms of treatment. The model will be adjusted
23 365 for the effects of blood pressure lowering on cardiovascular disease risk, costs and quality-adjusted-life
24 366 years (QALYs) to match the older population involved in this work. Costs of the therapies prescribed, side-
25 367 effects and acute and long term costs of cardiovascular events will be obtained within the trial and from
26 368 the literature. Quality of life on each treatment strategy will be obtained from the trial data using EQ-5D-5L,
27 369 and previous studies will inform utility values for cardiovascular disease health states and the impact of
28 370 side effects. The model will determine the cost per additional QALY gained of the medication reduction
29 371 intervention versus usual care and analyses will be conducted from a health and social services perspective.
30 372 The model will be run with a lifetime perspective, with costs and benefits discounted at a rate of 3.5%. A
31 373 value of information analysis will assess whether a further trial would be appropriate to reduce decision
32 374 uncertainty, and identify those parameters where more precise estimates would be most valuable and
33 375 should therefore be chosen as outcomes for such a trial.

34 376

35 377 **Ethics and dissemination**

36 378 This research involves older participants, some of whom may be considered vulnerable. Great care will be
37 379 taken to ensure all potential participants have the trial clearly explained, and are given sufficient time to
38 380 decide whether to give informed consent. This will include provision of simplified, participant information
39 381 sheets with large fonts, video infographics to explain the study and extended GP consultation periods for
40 382 explaining the study and taking informed consent. The protocol, informed consent form, participant
41 383 information sheet and all other participant facing material have been approved by the Research Ethics
42 384 Committee (South Central - Oxford A; ref 16/SC/0628), Medicines and Healthcare products Regulatory
43 385 Agency (ref 21584/0371/001-0001), host institution(s) and Health Research Authority. The study sponsor
44 386 reviewed and ensured all indemnity and insurance requirements for the trial were in place prior to the start
45 387 of recruitment.

1
2 388 All research outputs from this work will be published in peer-reviewed journals, presented at scientific
3 389 conferences and lay and social media (e.g. Twitter, blogs). 'Patient friendly' study summary documents and
4 390 infographics will be made available to all participants at the end of the trial via the study website.
5 391

6 392 *Current trial status*

7 393 The trial commenced recruitment on 10th April 2017 and is estimated to continue recruitment until
8 394 September 2018.
9 395

10 396 **Discussion**

11 397 Current guidelines in the UK suggest that doctors should ensure that patients are fully informed of the
12 398 benefits and risks of their prescribed medications and where appropriate, discuss the potential for
13 399 medication withdrawal in frail individuals with multi-morbidity.³⁵ This is difficult given consultation time
14 400 constraints and fear that de-prescribing might result in harm.³⁶ This is compounded by conflicting and
15 401 inconclusive evidence about the benefits and harms of treatment, and a lack of evidence about what will
16 402 happen if these treatments are reduced.
17 403

18 404 The ECSTATIC trial enrolled 1,067 younger participants aged 40-70 years, taking antihypertensives for
19 405 primary prevention of cardiovascular disease.¹⁸ The trial demonstrated that only 27% of participants were
20 406 able to maintain medication reduction throughout follow-up and at 3 months, systolic blood pressure was
21 407 on average 6 mmHg higher in the de-prescribing group. At 2 year follow-up, the risk of uncontrolled blood
22 408 pressure was significantly higher in those patients attempting to de-prescribe. Unlike the present study, the
23 409 medication reduction algorithm used did not encourage reintroduction of therapy if blood pressure was
24 410 persistently raised.
25 411

26 412 The DANTE study¹⁶ examined the effect of complete antihypertensive medication discontinuation in 385
27 413 patients over the age of 75 years and with mild cognitive deficits. After 16 weeks of follow-up, they
28 414 observed a 7/3 mmHg increase in blood pressure but no difference in overall cognition compound score or
29 415 quality of life between groups. A study by Van der Wardt and colleagues¹⁹ examined the feasibility trial
30 416 reducing antihypertensives in patients with dementia, but was only able to recruit 9 participants for the
31 417 withdrawal programme (1% recruitment rate) and a larger trial was deemed unfeasible. Similarly, the
32 418 OPTIMED trial³⁷ demonstrated in 95 participants that a broader de-prescribing approach is achievable in
33 419 patients living in nursing homes, but was unable to examine the effect on clinical outcomes due to
34 420 recruitment issues resulting on only 38% of the planned sample size being enrolled.
35 421

36 422 The OPTiMISE trial will target frail individuals with polypharmacy and co-morbidity, and aim to establish
37 423 whether a strategy of antihypertensive medication reduction is safe and acceptable to older patients. The
38 424 findings of this trial will support better patient-centred management plans for the prevention of
39 425 cardiovascular disease in older individuals and inform future de-prescribing trials in primary care.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Acknowledgements

The authors acknowledge the support of the Primary Care Clinical Trials Unit, staff from the NIHR CRNs including Thames Valley and South Midlands, Cambridge, Southampton, West Midlands (Central and South) and West of England, and Lucy Curtin for administrative support. Margaret Ogden and Anita Higham serve as patient representatives for the trial steering committee. Additional members of the trial steering committee are Prof Tom Robinson (chair), Prof Rod Taylor and Dr Peter Bower. Members of the data monitoring committee are Prof John Gladman (chair), Prof Una Martin and Dr Martyn Lewis. The sponsor and funder had no role in the study design, writing of the paper; or the decision to submit this protocol for publication, which was made jointly by the authors who have all approved the final manuscript. Finally, this work would not be possible without the support of the participating practices and participants.

Funding

This work receives joint funding from the National Institute for Health Research (NIHR) Oxford Collaboration for Leadership in Applied Health Research and Care (CLAHRC) at Oxford Health NHS Foundation Trust (ref: P2-501) and the NIHR School for Primary Care Research (SPCR; ref 335). JS and RJMcM have been funded by an NIHR Professorship (NIHR-RP-R2-12-015). FDRH acknowledges part support from the NIHR SPCR, the NIHR CLAHRC Oxford, and the NIHR Oxford Biomedical Research Centre (BRC). CH receives support from the NIHR SPCR and NIHR Oxford BRC. The views and opinions expressed are those of the authors and do not necessarily reflect those of the NHS, NIHR, or the Department of Health.

Competing interests

The authors declare no conflicts of interest.

Author's contributions

JS conceived, designed and secured funding for the study with JBu, ML, JBe, GF, CH, FDRH, SJ, PL, JM, EO, RP, MW, LMY and RJMcM. JS wrote the first draft. AN and LMY provided the sample size calculations and statistical analysis section. JBu provided the qualitative section. SJ provided the health economic section. All authors reviewed and edited the manuscript. ET is the trial manager. JS and RJMcM are co-chief investigators and will act as guarantors for this work.

Data sharing

Data sharing requests will be considered by the corresponding author.

References

1. Office for National Statistics. Mid-year populations estimates: Aging, fastest increase in the 'oldest old'. <http://www.ons.gov.uk>, 2010.
2. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* 2012;380(9836):37-43. doi: 10.1016/s0140-6736(12)60240-2 [published Online First: 2012/05/15]
3. Violan C, Foguet-Boreu Q, Roso-Llorach A, et al. 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. doi: 10.1186/1471-2458-14-530 [published Online First: 2014/06/03]
4. Sheppard JP, Singh S, Fletcher K, et al. 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. doi: 10.1136/bmj.e4535 [published Online First: 2012/07/14]
5. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *The New England journal of medicine* 2008;358(18):1887-98. doi: 10.1056/NEJMoa0801369 [published Online First: 2008/04/02]
6. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *The New England journal of medicine* 2015 doi: 10.1056/NEJMoa1511939 [published Online First: 2015/11/10]
7. McKee M, Britton A, Black N, et al. Interpreting the evidence: choosing between randomised and non-randomised studies. *BMJ (Clinical research ed)* 1999;319(7205):312-5.
8. van Deudekom FJ, Postmus I, van der Ham DJ, et al. External validity of randomized controlled trials in older adults, a systematic review. *PloS one* 2017;12(3):e0174053. doi: 10.1371/journal.pone.0174053 [published Online First: 2017/03/28]
9. Bejan-Angoulvant T, Saadatian-Elahi M, Wright JM, et al. 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. doi: 10.1097/HJH.0b013e328339f9c5 [published Online First: 2010/06/25]
10. Benetos A, Labat C, Rossignol P, et al. Treatment With Multiple Blood Pressure Medications, Achieved Blood Pressure, and Mortality in Older Nursing Home Residents: The PARTAGE Study. *JAMA internal medicine* 2015 doi: 10.1001/jamainternmed.2014.8012 [published Online First: 2015/02/17]
11. Tinetti ME, Han L, Lee DS, et al. Antihypertensive medications and serious fall injuries in a nationally representative sample of older adults. *JAMA internal medicine* 2014;174(4):588-95. doi: 10.1001/jamainternmed.2013.14764 [published Online First: 2014/02/26]
12. Fried TR, Tinetti ME, Towle V, et al. 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. doi: 10.1001/archinternmed.2011.32 [published Online First: 2011/03/02]
13. Schuling J, Gebben H, Veehof LJ, et al. Deprescribing medication in very elderly patients with multimorbidity: the view of Dutch GPs. A qualitative study. *BMC family practice* 2012;13:56. doi: 10.1186/1471-2296-13-56 [published Online First: 2012/06/16]
14. Scott IA, Anderson K, Freeman CR, et al. First do no harm: a real need to deprescribe in older patients. *The Medical journal of Australia* 2014;201(7):390-2. [published Online First: 2014/10/09]

- 1
2 499 15. Iyer S, Naganathan V, McLachlan AJ, et al. Medication withdrawal trials in people aged 65 years and
3 500 older: a systematic review. *Drugs & aging* 2008;25(12):1021-31. doi: 10.2165/0002512-200825120-00004
4 501 [published Online First: 2008/11/22]
- 5
6 502 16. Moonen JE, Foster-Dingley JC, de Ruijter W, et al. Effect of Discontinuation of Antihypertensive
7 503 Treatment in Elderly People on Cognitive Functioning--the DANTE Study Leiden: A Randomized Clinical Trial.
8 504 *JAMA internal medicine* 2015;175(10):1622-30. doi: 10.1001/jamainternmed.2015.4103 [published Online
9 505 First: 2015/08/25]
- 10
11 506 17. van der Wardt V, Harrison JK, Welsh T, et al. Withdrawal of antihypertensive medication: a systematic
12 507 review. *Journal of hypertension* 2017;35(9):1742-49. doi: 10.1097/hjh.0000000000001405 [published
13 508 Online First: 2017/05/10]
- 14
15 509 18. Luymes CH, Poortvliet RKE, van Geloven N, et al. Deprescribing preventive cardiovascular medication in
16 510 patients with predicted low cardiovascular disease risk in general practice - the ECSTATIC study: a cluster
17 511 randomised non-inferiority trial. *BMC medicine* 2018;16(1):5. doi: 10.1186/s12916-017-0988-0 [published
18 512 Online First: 2018/01/13]
- 19
20 513 19. van der Wardt V, Burton JK, Conroy S, et al. Withdrawal of antihypertensive therapy in people with
21 514 dementia: feasibility study. *Pilot and feasibility studies* 2018;4:29. doi: 10.1186/s40814-017-0221-0
22 515 [published Online First: 2018/01/18]
- 23
24 516 20. Nelson MR, Reid CM, Krum H, et al. Predictors of normotension on withdrawal of antihypertensive
25 517 drugs in elderly patients: prospective study in second Australian national blood pressure study cohort. *BMJ*
26 518 (*Clinical research ed*) 2002;325(7368):815. [published Online First: 2002/10/12]
- 27
28 519 21. Nelson MR, Reid CM, Krum H, et al. Short-term predictors of maintenance of normotension after
29 520 withdrawal of antihypertensive drugs in the second Australian National Blood Pressure Study (ANBP2).
30 521 *American journal of hypertension* 2003;16(1):39-45. [published Online First: 2003/01/09]
- 31
32 522 22. Clegg A, Bates C, Young J, et al. Development and validation of an electronic frailty index using routine
33 523 primary care electronic health record data. *Age and ageing* 2016;45(3):353-60. doi: 10.1093/ageing/afw039
34 524 [published Online First: 2016/03/06]
- 35
36 525 23. National Clinical Guideline C. National Institute for Health and Clinical Excellence Guidance CG127.
37 526 Hypertension: The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18
38 527 and 34. London: Royal College of Physicians (UK) 2011.
- 39
40 528 24. Mattu GS, Heran BS, Wright JM. Overall accuracy of the BpTRU--an automated electronic blood
41 529 pressure device. *Blood pressure monitoring* 2004;9(1):47-52. [published Online First: 2004/03/17]
- 42
43 530 25. Lahrman H, Cortelli P, Hilz M, et al. EFNS guidelines on the diagnosis and management of orthostatic
44 531 hypotension. *European journal of neurology* 2006;13(9):930-6. doi: 10.1111/j.1468-1331.2006.01512.x
45 532 [published Online First: 2006/08/26]
- 46
47 533 26. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version
48 534 of EQ-5D (EQ-5D-5L). *Quality of life research : an international journal of quality of life aspects of treatment,*
49 535 *care and rehabilitation* 2011;20(10):1727-36. doi: 10.1007/s11136-011-9903-x [published Online First:
50 536 2011/04/12]
- 51
52 537 27. Gallagher P, Ryan C, Byrne S, et al. STOPP (Screening Tool of Older Person's Prescriptions) and START
53 538 (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *International journal of clinical*
54 539 *pharmacology and therapeutics* 2008;46(2):72-83. [published Online First: 2008/01/26]

- 1
2 540 28. McManus RJ, Mant J, Bray EP, et al. Telemonitoring and self-management in the control of
3 541 hypertension (TASMINH2): a randomised controlled trial. *Lancet* 2010;376(9736):163-72. doi:
4 542 10.1016/s0140-6736(10)60964-6 [published Online First: 2010/07/14]
- 5
6 543 29. McManus RJ, Mant J, Haque MS, et al. Effect of self-monitoring and medication self-titration on systolic
7 544 blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized
8 545 clinical trial. *Jama* 2014;312(8):799-808. doi: 10.1001/jama.2014.10057 [published Online First:
9 546 2014/08/27]
- 10
11 547 30. Cuspidi C, Meani S, Lonati L, et al. Prevalence of home blood pressure measurement among selected
12 548 hypertensive patients: results of a multicenter survey from six hospital outpatient hypertension clinics in
13 549 Italy. *Blood pressure* 2005;14(4):251-6. doi: 10.1080/08037050500210765 [published Online First:
14 550 2005/08/30]
- 15
16 551 31. Tucker KL, Sheppard JP, Stevens R, et al. Self-monitoring of blood pressure in hypertension: A
17 552 systematic review and individual patient data meta-analysis. *PLoS medicine* 2017;14(9):e1002389. doi:
18 553 10.1371/journal.pmed.1002389 [published Online First: 2017/09/20]
- 19
20 554 32. Walker E, Nowacki AS. Understanding equivalence and noninferiority testing. *Journal of general internal*
21 555 *medicine* 2011;26(2):192-6. doi: 10.1007/s11606-010-1513-8 [published Online First: 2010/09/22]
- 22
23 556 33. Nathan A, Goodyer L, Lovejoy A, et al. 'Brown bag' medication reviews as a means of optimizing
24 557 patients' use of medication and of identifying potential clinical problems. *Family practice* 1999;16(3):278-
25 558 82. [published Online First: 1999/08/10]
- 26
27 559 34. Kaambwa B, Bryan S, Jowett S, et al. Telemonitoring and self-management in the control of
28 560 hypertension (TASMINH2): a cost-effectiveness analysis. *European journal of preventive cardiology*
29 561 2014;21(12):1517-30. doi: 10.1177/2047487313501886 [published Online First: 2013/08/31]
- 30
31 562 35. National Guideline Centre. National Institute for Health and Care Excellence: Clinical Guidelines.
32 563 Multimorbidity: Assessment, Prioritisation and Management of Care for People with Commonly Occurring
33 564 Multimorbidity [NICE Guideline 56]. London: National Institute for Health and Care Excellence (UK)
34
35 565 Copyright (c) National Institute for Health and Care Excellence, 2016. 2016.
- 36
37 566 36. Palagyi A, Keay L, Harper J, et al. Barricades and brickwalls--a qualitative study exploring perceptions of
38 567 medication use and deprescribing in long-term care. *BMC geriatrics* 2016;16:15. doi: 10.1186/s12877-016-
39 568 0181-x [published Online First: 2016/01/16]
- 40
41 569 37. Potter K, Flicker L, Page A, et al. Deprescribing in Frail Older People: A Randomised Controlled Trial. *PloS*
42 570 *one* 2016;11(3):e0149984. doi: 10.1371/journal.pone.0149984 [published Online First: 2016/03/05]
- 43
44 571 38. Sulter G, Steen C, De Keyser J. Use of the Barthel index and modified Rankin scale in acute stroke trials.
45 572 *Stroke; a journal of cerebral circulation* 1999;30(8):1538-41. [published Online First: 1999/08/06]
- 46
47 573 39. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle
48 574 aged African Americans. *The journal of nutrition, health & aging* 2012;16(7):601-8. [published Online First:
49 575 2012/07/28]
- 50
51 576 40. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people.
52 577 *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*
53 578 2005;173(5):489-95. doi: 10.1503/cmaj.050051 [published Online First: 2005/09/01]

1
2 579 41. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief
3 580 screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society* 2005;53(4):695-9.
4 581 doi: 10.1111/j.1532-5415.2005.53221.x [published Online First: 2005/04/09]

5
6 582 42. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to
7 583 treatment in chronic physical illness. *Journal of psychosomatic research* 1999;47(6):555-67. [published
8 584 Online First: 2000/02/08]

9 585

10
11 586

12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

587 **Tables**

588

589 **Table 1.** Trial inclusion and exclusion criteria

| Inclusion criteria |
|--|
| <ul style="list-style-type: none"> Participant is willing and able to give informed consent for participation in the trial. |
| <ul style="list-style-type: none"> Male or Female, aged 80 years or above. |
| <ul style="list-style-type: none"> 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). |
| <ul style="list-style-type: none"> 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, beta-blocker, vasodilator antihypertensives, centrally acting antihypertensives, direct renin inhibitors, adrenergic neurone blocking drugs or loop diuretics. |
| <ul style="list-style-type: none"> Stable dose of antihypertensive medications for at least four weeks prior to trial entry. |
| <ul style="list-style-type: none"> 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 |
| <ul style="list-style-type: none"> In the Investigator's opinion, is able and willing to comply with all trial requirements. |
| Exclusion criteria |
| <ul style="list-style-type: none"> A participant has heart failure due to LVSD and is on only ACE inhibitors/ARBs and/or beta-blockers and/or spironolactone (removing any of which would be contraindicated). |
| <ul style="list-style-type: none"> A participant has heart failure but has not had an echocardiogram since its onset (might have undiagnosed LVSD and a compelling need for ACE inhibitors/ARB and Beta-blockers). |
| <ul style="list-style-type: none"> Investigator deems that there is a compelling indication for antihypertensive medication continuation. |
| <ul style="list-style-type: none"> 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). |
| <ul style="list-style-type: none"> Suffered a myocardial infarction or stroke within the past 12 months. |
| <ul style="list-style-type: none"> Blood pressure being managed outside of primary care. |
| <ul style="list-style-type: none"> Unable to provide consent due to incapacity. |
| <ul style="list-style-type: none"> A participant with secondary hypertension or previous accelerated or malignant hypertension. |
| <ul style="list-style-type: none"> Participants who have participated in another research trial involving antihypertensive medication in the past 4 weeks. |
| 590 LVSD=Left ventricular systolic dysfunction; ACE inhibitor=Angiotensin Converting Enzyme inhibitor; |
| 591 ARB=Angiotensin II receptor blocker |

592 **Table 2.** Variables and schedule of data collection

| No. | Variable | Data source | | Schedule | |
|-----|---|---------------|------------------------------|----------|-----------|
| | | Medical notes | Measured/collected at clinic | Baseline | 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) ²⁶ | | ✓ | ✓ | ✓ |
| 17 | Functional independence (defined by modified Rankin Scale) ³⁸ | | ✓ | ✓ | |
| 18 | Frailty (according to the FRAIL scale) ³⁹ | | ✓ | ✓ | ✓ |
| 19 | Frailty (according to the frailty index and electronic frailty index) ^{22 40} | ✓ | ✓ | ✓ | ✓ |
| 20 | Cognitive function (defined by the Montreal Cognitive Assessment [MoCA]) ⁴¹ | | ✓ | ✓ | |
| 21 | Adherence to medication (according to the Medication Adherence Rating Scale (MARS) Questionnaire) ⁴² | | ✓ | ✓ | ✓ |
| 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 | ✓ | ✓ | | ✓ |

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

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

1
2 597 **Figure legends**

3 598

4 599 **Figure 1.** Trial flow diagram

5 600

6 601 *Monitoring of blood pressure at home will be encouraged but those not willing or able will still be
7 602 included in the trial. All participants will be asked to attend a safety monitoring visit with their GP/nurse
8 603 four weeks after baseline.

10 604 GP = General practitioner; BP = Blood pressure; HDL = High density lipoprotein; ICD = International
11 605 Statistical Classification of Diseases and Related Health Problems; CVD = Cardiovascular disease; eGFR =
12 606 estimated Glomerular Filtration Rate (eGFR); MARS = Medication Adherence Rating Scale; MOCA =
13 607 Montreal Cognitive Assessment

16
17 608 **Figure 2.** Medication reduction algorithm

18
19 609 **STOPP criteria**²⁷

20 610 Withdraw the one of the following medications if any of the ensuing contraindications are identified:

- 21 611 - Thiazide diuretic with a history of gout (may exacerbate gout).
- 22 612 - Beta-blocker in combination with verapamil (risk of symptomatic heart block).
- 23 613 - Non-cardioselective beta-blocker with chronic obstructive pulmonary disease (risk of
24 614 bronchospasm).
- 25 615 - Calcium channel blockers with chronic constipation (may exacerbate constipation).
- 26 616 - Use of diltiazem or verapamil with NYHA Class III or IV heart failure (may worsen heart failure).

29
30 617 **Figure 3.** Post medication reduction monitoring flow chart

31
32 618 Note: The full effects of most oral antihypertensives can last for up to 4-6 weeks. Frequent monitoring in
33 619 the initial 4 weeks after drug withdrawal is thus not required unless BP levels are extreme or there are
34 620 other clinical concerns (see above). Where systolic/diastolic BP values fall into different categories, consider
35 621 the higher value. BP should be taken as the averaged second and third measurements using a validated
36 622 monitor. Standard clinical care/monitoring should align with NICE recommendations.²³

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

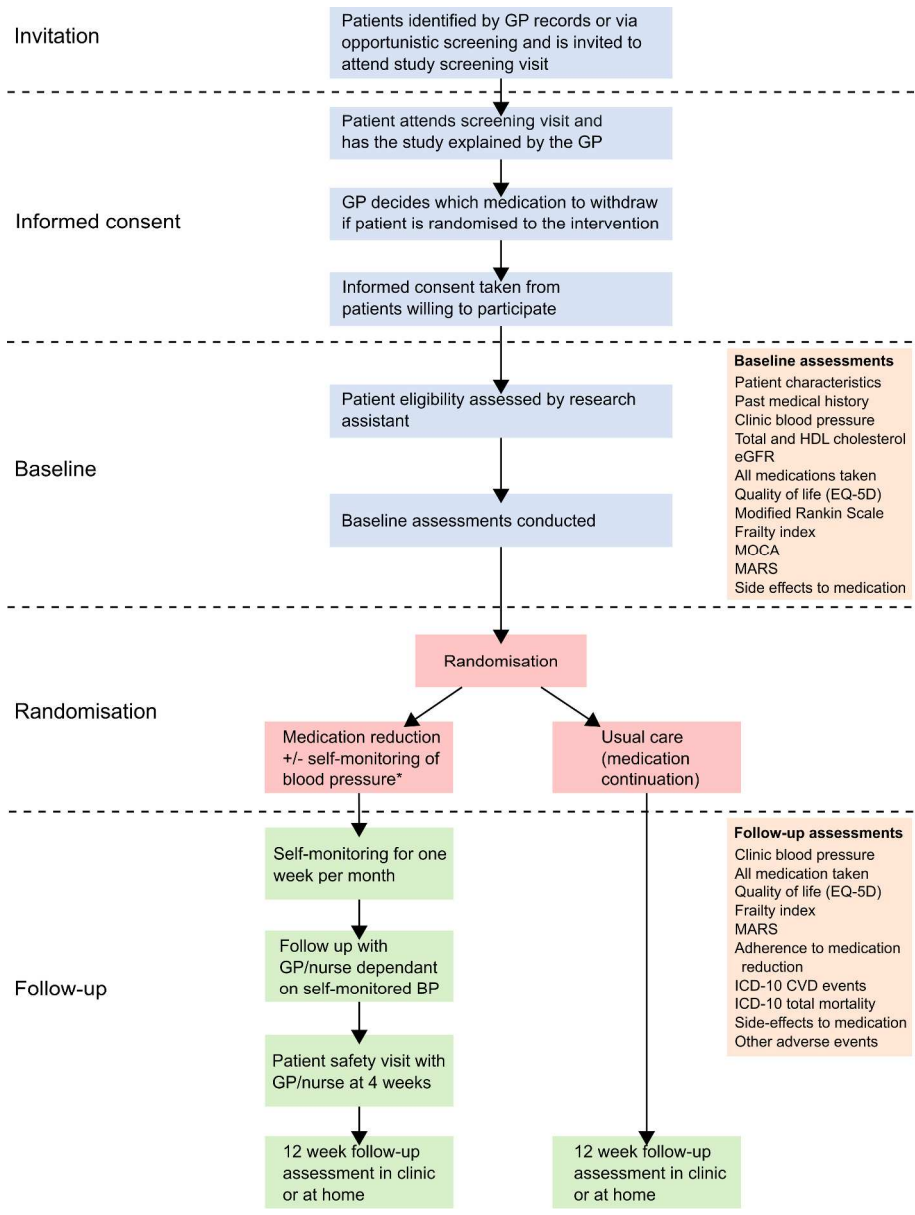


Figure 1

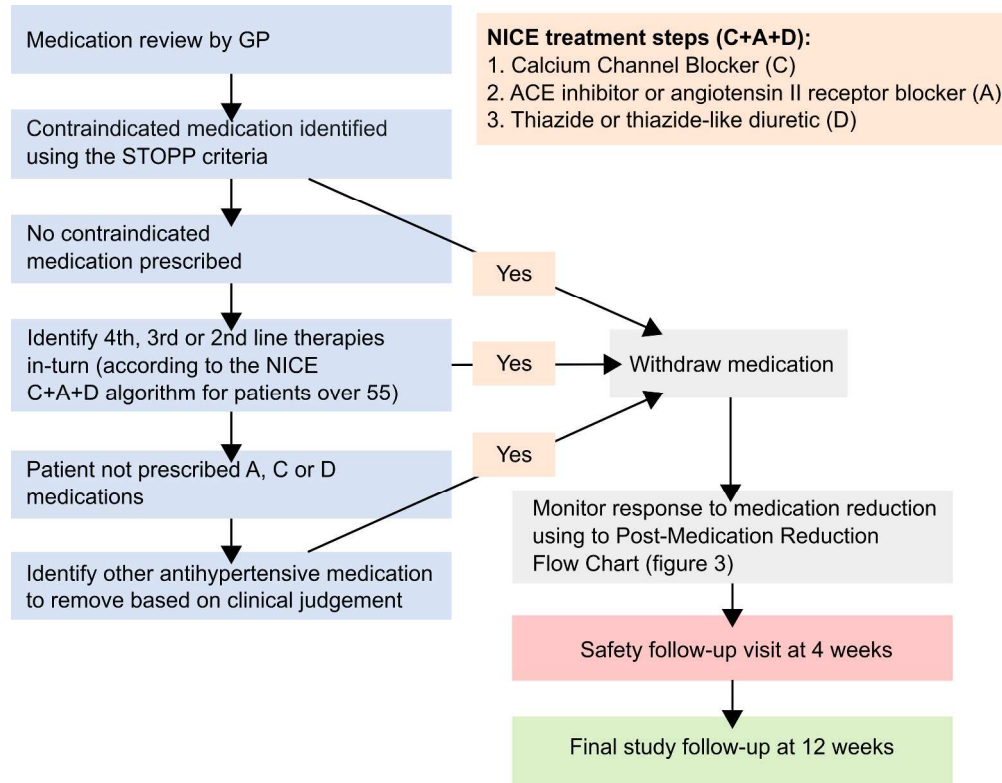


Figure 2

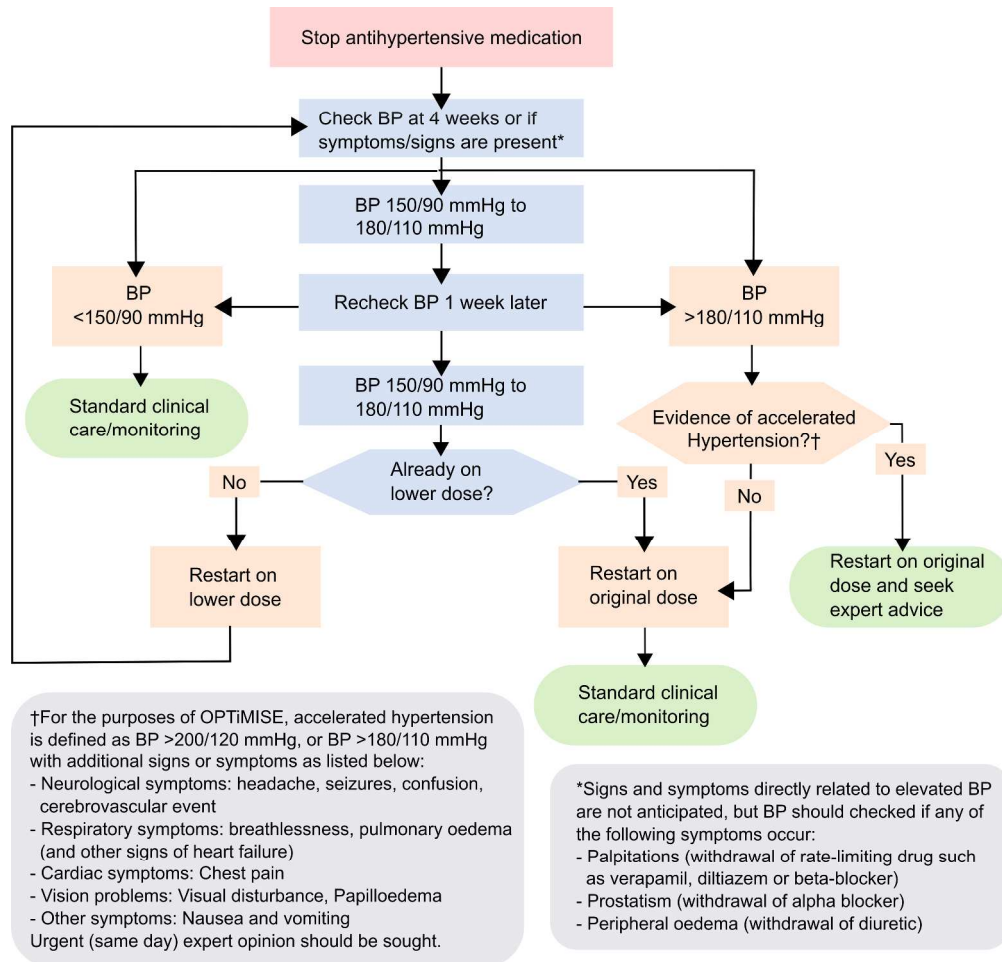


Figure 3



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Page in protocol |
|---|---------|--|------------------|
| Administrative information | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | n/a |
| Protocol version | 3 | Date and version identifier | n/a |
| Funding | 4 | Sources and types of financial, material, and other support | 12 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1, 12 |
| | 5b | Name and contact information for the trial sponsor | 1 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 12 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 12 |
| Introduction | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 3 |
| | 6b | Explanation for choice of comparators | 3 |
| Objectives | 7 | Specific objectives or hypotheses | 3-4 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 4 |
| Methods: Participants, interventions, and outcomes | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 4 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will | 4, table 1 |

| | | | |
|---|-----|--|----------|
| | | perform the interventions (eg, surgeons, psychotherapists) | |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 5 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | Figure 3 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 6-7 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 7 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 4-5 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Figure 1 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 8 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 5 |
| Methods: Assignment of interventions (for controlled trials) | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 6 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 6 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 6 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 6 |

| | | | |
|---|-----|--|-----|
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 6 |
| Methods: Data collection, management, and analysis | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 5-7 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 7 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 6 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 8 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 8 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 8 |
| Methods: Monitoring | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 9 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 9 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 9 |
| Ethics and dissemination | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 10 |

| | | | |
|-------------------------------|-----|---|-----|
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | n/a |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 5 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | n/a |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 12 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 12 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | n/a |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 10 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | n/a |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | n/a |
| Appendices | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | n/a |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

OPTimising Treatment for MIld Systolic hypertension in the Elderly (OPTiMISE): protocol for a randomised controlled non-inferiority trial

| | |
|---------------------------------|--|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2018-022930.R2 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 10-Aug-2018 |
| Complete List of Authors: | Sheppard, James; University of Oxford, Nuffield Department of Primary Care Health Sciences Burt, Jenni; University of Cambridge, Cambridge Centre for Health Services Research Lown, Mark; University of Southampton Temple, Eleanor; University of Oxford, Nuffield Department of Primary Care Health Sciences Benson, John; University of Cambridge, GP and Primary Care Research Unit Ford, Gary; Oxford University Hospitals NHS Foundation Trust, Oxford Academic Health Science Network Heneghan, Carl; Oxford University, Primary Health Care Hobbs, Richard; University of Oxford, Nuffield Department of Primary Care Health Sciences Jowett, Sue; University of Birmingham, Health Economics Unit Little, Paul; University of Southampton, Primary Care and Population Science; Mant, Jonathan; University of Cambridge, General Practice and Primary Care Research Unit Mollison, Jill; University of Oxford, Nuffield Department of Primary Care Health Sciences Nickless, Alecia; University of Oxford, Nuffield Department of Primary Care Health Sciences Ogburn, Emma; University of Oxford, Payne, Rupert; University of Bristol, Centre for Academic Primary Care Williams, Marney; Patient and public involvement representative Yu, Ly-Mee; University of Oxford, Department of Primary Care Health Sciences McManus, Richard; University of Oxford, Dept of Primary Care Health Sciences |
| Primary Subject Heading: | General practice / Family practice |
| Secondary Subject Heading: | Cardiovascular medicine, Geriatric medicine, Health services research |
| Keywords: | Multi-morbidity, Cardiovascular disease, Frailty, Antihypertensive, De-prescribing |
| | |

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.

OPTIMISE video infographic V1.1 14.03.17.mp4

SCHOLARONE™
Manuscripts

For peer review only

1
2
3
4
5 4 James P Sheppard,¹ Jenni Burt,² Mark Lown,³ Eleanor Temple,¹ John Benson,⁴ Gary A Ford,¹ Carl Heneghan,¹
6 5 FD Richard Hobbs,¹ Sue Jowett,⁵ Paul Little,³ Jonathan Mant,⁴ Jill Mollison,¹ Alecia Nickless,¹ Emma Ogburn,¹
7 6 Rupert Payne,⁶ Marney Williams,⁷ Ly-Mee Yu,¹ and Richard J McManus¹
8 7

9 8 ¹Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

10 9 ²The Healthcare Improvement Studies Institute, University of Cambridge, Cambridge, UK

11 10 ³Primary Care Research Group, University of Southampton, Southampton, UK

12 11 ⁴Primary Care Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

13 12 ⁵Institute of Applied Health Research, University of Birmingham, Birmingham, UK

14 13 ⁶Centre for Academic Primary Care, University of Bristol, Bristol, UK

15 14 ⁷Patient and public involvement representative, London, UK
16 15

17 16 James P Sheppard

18 17 james.sheppard@phc.ox.ac.uk

19 18 +44 1865 617192

20 19 Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care Building, Radcliffe
21 20 Observatory Quarter, University of Oxford, Oxford, OX2 6GG, UK
22 21

23 22 University of Oxford

24 23 Ms Heather House

25 24 Clinical Trials and Research Governance, Joint Research Office, Block 60, Churchill Hospital,
26 25 University of Oxford, Oxford, OX3 7LE
27 26

28 27 ctrg@admin.ox.ac.uk
29 28

30 29 ! 4,208 (excluding title page, abstract, references, tables and figures)

31 30 " # # 2

32 " # 3
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

#

Recent evidence suggests that larger blood pressure reductions and multiple antihypertensive drugs may be harmful in older people, particularly frail individuals with polypharmacy and multi-morbidity. However, there is a lack of evidence to support de-prescribing of antihypertensives, which limits the practice of medication reduction in routine clinical care. The aim of this trial is to examine whether antihypertensive medication reduction is possible in older patients without significant changes in blood pressure control at follow-up.

This trial will use a Primary Care based, open label, randomised controlled trial design. A total of 540 participants will be recruited, aged ≥ 80 years, with systolic blood pressure < 150 mmHg and receiving ≥ 2 antihypertensive medications. Participants will have no compelling indication for medication continuation and will be considered to potentially benefit from medication reduction due to existing polypharmacy, co-morbidity and frailty. Following a baseline appointment, individuals will be randomised to a strategy of medication reduction (intervention) with optional self-monitoring or usual care (control). Those in the intervention group will have one antihypertensive medication stopped. The primary outcome will be to determine if a reduction in medication can achieve a proportion of participants with clinically safe blood pressure levels at 12 week follow-up (defined as a systolic blood pressure < 150 mmHg) which is non-inferior (within 10%) to that achieved by the usual care group. Qualitative interviews will be used to understand the barriers and facilitators to medication reduction. The study will use economic modelling to predict the long term effects of any observed changes in blood pressure and quality-of-life.

The protocol and written information has been approved by a Research Ethics Committee, medicines regulatory authority (MHRA), and national and local health research authorities. All research outputs will be published in peer-reviewed journals and presented at national and international conferences.

EudraCT 2016-004236-38; ISRCTN97503221

! 300 (max 300)

\$ % Multi-morbidity, cardiovascular disease, frailty, antihypertensive, de-prescribing

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 61 • This will be the first UK randomised controlled trial to compare a strategy of antihypertensive
62 medication reduction to usual care in primary care.
- 63 • The pragmatic trial design, with broad inclusion criteria, will make findings of the study externally valid
64 in routine clinical practice.
- 65 • Allowing the attending GP to choose the medication to be reduced will maximise external validity of
66 the trial results but precludes the possibility of blinding the participants and investigators.
- 67 • The trial will be powered to detect a non-inferior difference in blood pressure control at follow-up, but
68 not necessarily secondary outcomes such as differences in rates of cardiovascular disease, adverse
69 events and quality of life.

For peer review only

1
2 70
3 71 The general population is ageing¹ and, consequently, the number of people living with age-related chronic
4 72 conditions is increasing.² Hypertension is the number one co-morbid condition in older people with
5 73 multiple chronic conditions³ and 52% of those aged ≥ 80 years are prescribed two or more antihypertensive
6 74 drugs (equivalent to approximately 1.25 million people in the UK).⁴ Blood pressure lowering has been
7 75 shown to be effective at preventing stroke and cardiovascular disease in healthy individuals aged ≥ 80 years
8 76 with stage 2 hypertension (systolic blood pressure of >160 mmHg) and high risk stage 1 hypertension.^{5,6}
9 77 However, as with many trials,^{7,8} these studies included healthier populations with lower polypharmacy and
10 78 multi-morbidity than might be expected in the general elderly population. In addition, there is evidence to
11 79 suggest that larger blood pressure reductions and multiple antihypertensive prescriptions may be harmful
12 80 in older people.^{9,10} Evidence from observational studies also suggests that higher intensity blood pressure
13 81 treatment is associated with increased risk of falls in older people,¹¹ although this is also disputed.⁵

14 82
15 83 Some patients consider the increased risk of falls and other adverse events to be as important as the risk of
16 84 myocardial infarction or stroke, particularly those taking medications for primary prevention of
17 85 cardiovascular disease.¹² Thus, decisions over blood pressure lowering in the elderly, particularly the frail
18 86 elderly, require the weighing of harms and quality of life. However, clinicians can often struggle to stop
19 87 prescribing medication due to a perceived lack of evidence, fear of the reaction of other prescribers, fear of
20 88 precipitating events such as stroke or angina and concern that patients will feel their care is being cut.^{13,14}

21 89
22 90 There is limited evidence from randomised trials examining the safety of antihypertensive medication
23 91 reduction or withdrawal.¹⁵⁻¹⁹ The HYVET trial⁵ enrolled some patients on antihypertensive treatment who
24 92 were then randomised to placebo (effectively complete medication withdrawal) and the ANBP2 trial
25 93 investigators followed up participants who withdrew medication during the trial run-in period but who
26 94 were not randomised into the trial. They found younger patients with lower baseline blood pressure and
27 95 fewer drug prescriptions were more likely to sustain medication withdrawal at 12 month follow-up.^{20,21}
28 96 However, there are few trials comparing a specified strategy of antihypertensive medication reduction with
29 97 usual care in terms of effects on blood pressure control and quality of life.¹⁷ In addition, there are no
30 98 previous economic modelling studies of a strategy of medication reduction in the elderly.

31 99
32 100 The aim of this work will be to examine whether antihypertensive medication reduction in patients with
33 101 controlled systolic hypertension (≤ 150 mmHg) who are being prescribed two or more antihypertensives is
34 102 possible without significant changes in blood pressure control at follow-up.

35 103
36 104

37 105 *Aims and outcomes*

38 106 The aim of this study is to determine whether antihypertensive medications can be safely reduced without
39 107 systolic blood pressure increasing beyond what is clinical acceptable at follow-up.

40 108 The primary outcome is the proportion of participants with clinically acceptable levels at 12 week follow-up
41 109 (defined as a systolic blood pressure <150 mmHg) Secondary outcomes will examine:

- 42 110 • The proportion of participants in the intervention arm who maintain medication reduction through
43 111 to follow-up (*i.e.* are *not* restarted on therapy).
- 44 112 • The difference in quality of life (according to EQ-5D-5L) between groups at 12 week follow-up.
- 45 113 • The difference in frailty (according to the frailty index)²² between the two groups at 12 week follow-
46 114 up.

47
48
49
50
51
52
53
54
55
56
57
58
59

- 115 • The difference in the change in mean clinic systolic blood pressure (from baseline) between the two
- 116 groups at 12 week follow-up.
- 117 • The difference in reported side effects to medication between the two groups at 12 week follow-up
- 118 (including coughs, dizziness, syncope, and ankle swelling).
- 119 • The difference in routinely reported serious adverse events between the two groups at 12 week
- 120 follow-up (hospitalisation due to falls, myocardial infarction, stroke or all-cause mortality).

121

122 *Design*

123 This trial will use a Primary Care based, open label, randomised controlled, two-parallel groups, non-
124 inferiority trial design, recruiting 540 participants with controlled blood pressure (systolic <150 mmHg) on
125 two or more antihypertensive treatments. Participants will be randomised to a strategy of medication
126 reduction (intervention) or usual care (control) and followed-up for 12 weeks (see figure 1). Embedded
127 qualitative and economic analyses will examine barriers and facilitators to medication reduction and the
128 cost effectiveness of the approach.

129

130 *Trial participants*

131 Patients eligible for the trial will be aged ≥ 80 years, with systolic blood pressure <150mmHg (current UK
132 guideline recommendation)²³ receiving ≥ 2 antihypertensive medications. They will have no compelling
133 indication for medication continuation and in the opinion of the attending GP, may potentially benefit from
134 medication reduction due to existing polypharmacy, co-morbidity and/or frailty (table 1).

135

136 Participants will be identified and recruited from general practices via the UK Clinical Research Network
137 (CRN). Potentially eligible patients will be identified by trained practice staff searching practice-based
138 electronic disease registers using a standardised strategy. GPs will be asked to check the search results and
139 remove people whom they believe to be unsuitable to participate in the study. Remaining potentially
140 eligible patients will be sent letters of invitation from their GP and those expressing an interest in the trial
141 will be asked to attend a screening and baseline appointment. Patients not responding to the first invitation
142 will receive one reminder letter (up to four weeks after the first letter). Other potentially eligible patients
143 may also be approached opportunistically by a member of the clinical care team. Those who do not wish to
144 take part will be asked to fill in a short questionnaire detailing their reasons.

145

146 *Baseline visit*

147 Eligible patients will have informed consent taken by the GP. During the consent appointment, the GP will
148 show a two-minute study video infographic (see supplementary material) and go through the participant
149 information sheet explaining the exact nature of the trial. Having had a chance to ask questions, those
150 individuals willing to participate will give written informed consent by means of a participant dated
151 signature and dated signature of the GP who presented and obtained the informed consent.

152

153 Some participants will be invited to have their interview audio-recorded for qualitative analysis during their
154 study visits. Those who are interested will be asked to sign a response slip prior to meeting the GP. Consent
155 to audio recordings will not have a bearing on an individual's care or eligibility for the main trial.

156

157 Those giving informed consent will be screened using the criteria in table 1 and undergo baseline
158 measurements and randomisation by a member of the research team via participant questionnaires and a
159 detailed notes review (table 2).

160

161 # &' Trial inclusion and exclusion 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, beta-blocker, vasodilator antihypertensives, centrally acting antihypertensives, direct renin inhibitors, adrenergic neurone blocking drugs or loop diuretics.
-
- Stable dose of 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
-
- In the Investigator's opinion, is able and willing to comply with all trial requirements.
-
- (
-
- A participant has heart failure due to 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 ACE inhibitors/ARB and Beta-blockers).
-
- Investigator deems that there is a compelling indication for antihypertensive medication continuation.
-
- 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).
-
- Suffered a myocardial infarction or stroke within the past 12 months.
-
- Blood pressure being managed outside of primary care.
-
- Unable to provide consent due to incapacity.
-
- A participant with secondary hypertension or previous accelerated or malignant hypertension.
-
- Participants who have participated in another research trial involving antihypertensive medication in the past 4 weeks.
-

162 LVSD=Left ventricular systolic dysfunction; ACE inhibitor=Angiotensin Converting Enzyme inhibitor;

163 ARB=Angiotensin II receptor blocker

164 #)' Variables and schedule of data collection

| | " | ' | * # | + | | | |
|----|---|---|-----|---------------|------------------------------|----------|-----------|
| | | | | Medical notes | Measured/collected at clinic | Baseline | 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) ²⁴ | | | | ✓ | ✓ | ✓ |
| 17 | Functional independence (defined by modified Rankin Scale) ²⁵ | | | | ✓ | ✓ | |
| 18 | Frailty (according to the FRAIL scale) ²⁶ | | | | ✓ | ✓ | ✓ |
| 19 | Frailty (according to the frailty index and electronic frailty index) ^{22 27} | | | ✓ | ✓ | ✓ | ✓ |
| 20 | Cognitive function (defined by the Montreal Cognitive Assessment [MoCA]) ²⁸ | | | | ✓ | ✓ | |
| 21 | Adherence to medication (according to the Medication Adherence Rating Scale (MARS) Questionnaire) ²⁹ | | | | ✓ | ✓ | ✓ |
| 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 | | | ✓ | ✓ | | ✓ |

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

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

1
2 169 Blood pressure will be measured in a standardised fashion using the clinically validated³⁰ BpTRU blood
3 170 pressure monitor which automatically records six blood pressure measurements at one minute intervals.
4 171 Blood pressure readings will be taken in the left arm (where appropriate) after participants have been
5 172 seated for at least five minutes of rest, using an appropriate sized cuff. The mean of the 2nd and 3rd readings
6 173 will be used to define the primary outcome. To test for orthostatic hypotension, two further readings will
7 174 be taken in the standing position after one and three minutes.³¹ Only the research facilitator/nurse will be
8 175 present during the blood pressure measurements. Orthostatic hypotension will be defined as a ≥ 20 mmHg
9 176 drop in systolic blood pressure within three minutes of standing.
10 177

11
12 178 All data will be collected via an electronic case report form (eCRF) linked to the study database. Participants
13 179 will be given the option to enter responses to questionnaires themselves or with assistance from the
14 180 research team. Where questionnaires are not validated for use on a tablet computer,²⁴ or where individuals
15 181 are not comfortable using one, paper copies will be made available for completion.
16 182

17 183 *Randomisation*

18
19 184 Consenting participants will be individually randomised (1:1 allocation ratio) to one of two study arms using
20 185 a fully validated web-based system (Sortition[®]) with manual telephone back up. Participants will not be
21 186 randomised until after consent has been taken and baseline assessments have been completed. A
22 187 computer generated non-deterministic algorithm, minimising on practice and baseline systolic blood
23 188 pressure will be used to ensure these covariates are balanced between the two intervention arms.
24 189

25
26 190 The study will use an open label design, so patients and practitioners will not be blinded to the intervention
27 191 or study endpoints. Therefore, codebreaking will not be necessary. The statistical analysis will be
28 192 performed blind to patient allocation.
29 193

30 194 *Intervention group*

31
32 195 Participating GPs will review each participant's antihypertensive medication regimen prior to the baseline
33 196 appointment, and decide which medication should be removed if they are randomised to the intervention
34 197 arm of the trial. The choice of medication to be withdrawn will be at the discretion of the GP, but their
35 198 decision will be informed by an individual's co-morbidities and existing guidelines, where appropriate
36 199 (figure 2). Specifically, participating GPs will be encouraged to identify previously unrecognised
37 200 contraindications to medication, defined by the STOPP criteria.³² In the absence of these, or a strong clinical
38 201 rationale for continuing despite a STOPP criteria being met, GPs will be recommended to reduce
39 202 antihypertensive medications in reverse of the NICE C+A+D algorithm for older patients (figure 2).²³ All
40 203 participants in the trial will remain on at least one antihypertensive.
41 204

42
43 205 Once a medication has been removed, GPs or other appropriate, delegated healthcare professionals will
44 206 closely monitor the participant's response to medication reduction: they will be given advice about what
45 207 and when to monitor (figure 3), but this schedule will be flexible. All participants will be expected to return
46 208 for at least one routine safety follow-up visit, and further visits may be required if blood pressure is raised
47 209 (≥ 150 mmHg), or adverse events occur. Where blood pressure is persistently raised, GPs will be expected to
48 210 re-adjust medication (dose or type), rendering the likelihood of a serious adverse event occurring as a
49 211 result of the intervention very low.
50 212

51 213 *Self-monitoring*

1
2 214 All participants randomised to the medication reduction arm of the trial will be given the option to self-
3 215 monitor their blood pressure at home. Those accepting will be trained using protocols developed in the
4 216 previous TASMIN trials^{33 34} and will be given simple and clear instructions to contact their GP if their blood
5 217 pressure rises above what is considered clinically safe (e.g. home systolic blood pressure >145mmHg on all
6 218 readings taken in a week). Participants will be advised to self-monitor (or have a carer monitor) at least 4
7 219 times per week in the last week of each month of follow-up (weeks 4, 8 and 12), although they can monitor
8 220 more frequently if they wish. Differential use of self-monitoring in the intervention group, or indeed in the
9 221 control group (many patients now self-monitor routinely)³⁵ is not expected to impact on the study results,
10 222 since there is good evidence that self-monitoring only affects blood pressure levels if used in combination
11 223 with a co-intervention.³⁶ All other clinical care will continue as usual.
12
13 224

14 225 *Control group*

15 226 Those allocated to the control arm of the study will continue usual clinical care (i.e. they will continue to
16 227 take antihypertensive medications as prescribed and will not self-monitor unless already doing so). No
17 228 other medication changes will be mandated and participating GPs will be asked to manage all other care
18 229 according to usual clinical practice.
19
20 230

21 231 *Follow-up visits*

22 232 Participants will attend one research follow-up clinic, 12 weeks (± 2 weeks) after baseline and those in the
23 233 intervention will attend one additional safety visit after four weeks (± 2 weeks) (figure 1). A period of four
24 234 weeks is expected to be sufficiently long enough to assess the impact of antihypertensive medication
25 235 reduction, since these drugs usually take approximately four weeks to 'wash out' of a patient's system.
26 236 Earlier safety visits are not recommended since they could provide false reassurance that blood pressure is
27 237 within safe limits if the withdrawn drug has not washed out of the participant's system.
28
29 238

30 239 The follow-up assessments will include standardised blood pressure measurement (for assessment of the
31 240 primary outcome), questionnaire assessments and adherence to the trial medication regime, side effects
32 241 and adverse events (table 2). Where possible, all participants will be flagged for mortality and hospital
33 242 admissions using NHS patient tracking services, permitting long-term follow-up for up to 5 years after the
34 243 trial has finished.
35
36 244

37 245 Each participant has the right to withdraw from the trial at any time. We will ask all participants to attend a
38 246 follow-up visit as far as is practicable, regardless of whether medication is re-introduced to participants in
39 247 the intervention group, or a participant in the control group has medication withdrawn. Unless a
40 248 participant withdraws consent, vital status will be assessed even where an individual has been lost to
41 249 follow-up (for instance moved away). If given, the reason for withdrawal will be recorded in the eCRF.
42
43 250

44 251 *Internal feasibility study*

45 252 A two-stage internal feasibility study will be conducted to examine methods of patient invitation and rates
46 253 of recruitment, before proceeding with the main trial. The first feasibility phase will last for a minimum of
47 254 three months and aim to recruit approximately 25 participants from a minimum of 3-5 practices. The aim
48 255 will be to establish whether or not anyone will be willing to participate in the study.
49
50 256

51 257 The second feasibility phase will focus on recruitment rates for the main trial and whether the intended
52 258 sample size is likely to be met during the recruitment period. This phase will have a recruitment target of 75
53 259 participants from ten practices over 6 months, giving a total sample for the feasibility study of 100
54
55
56
57
58
59
60

1
2 260 participants. A recruitment rate of 15% of invitations sent is expected. The following actions will be
3 261 considered to address varying rates of recruitment at the end of the feasibility phases:
4 262 - If ≥ 100 participants are recruited – trial will proceed as planned
5 263 - If 75-99 participants are recruited – recruitment materials/method will be re-examined and edited
6 264 where necessary following discussions with stakeholders and patient and public involvement
7 265 representatives.
8 266 - If 50-74 participants are recruited – the allocation of resources and recruitment criteria will be re-
9 267 examined using information gathered from concurrent qualitative work.
10 268 - If < 50 participants are recruited – the Trial Steering Committee (TSC) will decide, in discussion with
11 269 the Data Monitoring and Ethics Committee (DMEC) and the funders, whether the trial should be
12 270 stopped due to futility.
13
14 271

15 272 *Sample size calculation*

16 273 Assuming that 100% of participants in the usual care group, and 96% of those in the medication reduction
17 274 group have controlled systolic blood pressure levels (< 150 mmHg) at follow-up, approximately 540
18 275 participants will be required to detect a non-inferior difference in systolic blood pressure control between
19 276 groups. Calculations assume a 10% non-inferiority margin, 90% power, 2.5% 1-sided level of significance,
20 277 10% loss to follow-up and a 10% dilution effect due to cross-over between arms. There is no existing
21 278 precedent for an appropriate margin of non-inferiority in this type of trial, but 10% was deemed useful to
22 279 inform future doctor-patient discussions about medication reduction: if the non-inferiority margin is met, it
23 280 will suggest that for every ten patients who have their medication reduced, at least nine will still have
24 281 controlled blood pressure at 12 week follow-up.
25
26 282

27 283 *Statistical analysis*

28 284 A detailed statistical analysis plan will be agreed prior to the end of the trial. The primary and secondary
29 285 analyses will be by intention to treat (ITT), unless stated otherwise. The primary analysis will be a non-
30 286 inferiority analysis by means of the “two one-sided test” (TOST) procedure,³⁷ whereby the 95% confidence
31 287 interval for the relative risk of participants with systolic blood pressure at 12 weeks below 150 mmHg
32 288 between the medication reduction group and the usual care group is calculated. This will be obtained by
33 289 means of a generalised linear mixed effects model with GP surgery included as a random effect and
34 290 baseline blood pressure as a fixed effect. If the lower limit of the confidence interval is more than 0.9 (equal
35 291 to a risk difference of 10%) then the research hypothesis that medication reduction will be non-inferior in
36 292 terms of blood pressure control to usual care will be accepted. As a secondary analysis of the primary
37 293 outcome, a per-protocol (PP) analysis will be performed, since ITT can be anticonservative for a non-
38 294 inferiority hypothesis.³⁷ Participants who received the medication reduction intervention in the PP analysis
39 295 will be defined as a participant in the medication reduction arm who maintained their medication reduction
40 296 throughout the 12 week follow-up period.
41
42 297

43 298 Secondary analyses will examine the proportion of participants in the medication reduction arm who
44 299 maintained their medication reduction throughout the 12 week follow-up period. Secondary outcomes will
45 300 be analysed by means of linear mixed effects models, adjusting for the baseline level of the outcome and
46 301 baseline systolic blood pressure and including practice as a random effect: systolic blood pressure, EQ-5D-
47 302 5L and the Frailty index/frail scale. The difference in the rate of side effects and adverse events between
48 303 the medication reduction and usual care arms will be analysed by means of a logistic mixed effects model
49 304 adjusting for baseline systolic blood pressure and including practice as a random effect.
50
51 305

1
2 306 Exploratory subgroup analyses of blood pressure control, change in blood pressure and maintenance of
3 307 medication reduction will be conducted by different levels of baseline frailty, functional independence,
4 308 cognitive function, number of medications prescribed at baseline and number of co-morbidities at baseline.

5 309

6 310

, ,

7
8 311 This protocol was developed through discussions with older patients and carers and members of an AgeUK
9 312 day centre. MW is a stroke survivor with experience as a volunteer on the elderly ward of Charing Cross
10 313 Hospital. She was consulted on the suitability and design of the trial and is a member of the trial
11 314 management group. Methods of patient approach, including the design of the video infographic, patient
12 315 information sheet and consent form were all reviewed by patient representatives prior to formal approval.
13 316 The TSC includes two independent patient representatives responsible for overseeing the conduct of the
14 317 trial.

15 318

16 319

17
18 320 Adverse events that are observed by an investigator or reported by the participant will be recorded on the
19 321 AE log at any time during the study but AEs will be specifically asked about at the 12 week follow up.
20 322 Serious adverse events (SAEs) will be reported to the coordinating centre within 24 hours of discovery or
21 323 notification of the event. All SAE reports will be reviewed by the DMEC chair on a monthly basis, and by the
22 324 full DMEC at meetings held every 6 months. The DMEC will include a geriatrician, statistician and consultant
23 325 clinical pharmacologist. They will be responsible for safeguarding trial participants, monitoring emerging
24 326 trial data including identifying any trends, such as increases in unexpected events, and take appropriate
25 327 action where necessary.

26 328

27
28 329 All adverse events labelled possibly, probably or definitely related will be considered as related to the
29 330 intervention. Since there are no sections of the Summary of medicinal Product Characteristics, or previous
30 331 clinical studies which detail expected adverse events as a result of medication withdrawal, all SAEs at least
31 332 possibly related, and not as a result of re-introduction of withdrawn medication, will be considered
32 333 unexpected and reported as SUSARs. Fatal and life-threatening SUSARs will be reported by the chief
33 334 investigator to the relevant Competent Authority and Research Ethics Committee no later than 7 calendar
34 335 days after the Sponsor or delegate is first aware of the reaction. All other SUSARs will be reported within 15
35 336 calendar days.

36 337

37 338

- , #

38 339 *Study 1: interviews with doctors and patient*

39 340 Face-to-face interviews with GPs and patients will be conducted to generate understanding about the
40 341 barriers and facilitators to antihypertensive medication reduction. Informed consent will be sought from
41 342 approximately 15 GPs to provide a broad range of opinion from varying practice sizes (small to large) and
42 343 settings (rural to urban). Participating GPs will also be asked to identify up to 15 patients for interview,
43 344 based on the same inclusion criteria as those applied to participants in the main trial.

44 345

45 346 Interviews with GPs will use a chart-stimulated recall approach to explore the factors which influence their
46 347 treatment choices in older hypertensive patients. Anonymised electronic health records will be used to
47 348 focus discussions about how GPs would feel about reducing antihypertensive medications. Interviews with
48 349 patients will use 'brown bag' medication review techniques³⁸ to create a complete record of medication
49 350 held, with a commentary on usage from the participants' perspective. Diagrammatic elicitation techniques
50 351 will be used to complete a relational map outlining participants' circumstances and how these relate to the

1 352 medications taken. These sketches will be used as the basis for a discussion on the implications of
2 353 withdrawing antihypertensive medications, and what this “gap” might mean for the patient.

3 354

4 355 All interviews will be transcribed verbatim, stored and organised using NVivo software (QSR International
5 356 Pty Ltd, Doncaster, Victoria, Australia). Interview and visual data from GP and patient interviews will be
6 357 subjected to thematic analysis, with a particular orientation to exploring clinical and patient perspectives
7 358 on the barriers and facilitators to reducing antihypertensives.

8 359

9 360 *Study 2: Assessment of trial recruitment and data collection procedures*

10 361 The aim of the second qualitative study will be to explore how information is presented within recruitment
11 362 appointments and how this might impact on consent to participate, with a view to ensuring robust trial
12 363 procedures using an iterative process. This will be achieved by audio-recording (with consent) up to 75
13 364 consultations between GPs or research assistants and eligible patients.

14 365

15 366 Thematic analysis will be undertaken on a sample of around 15-20 consultations comprising patients who
16 367 did, or did not consent to participate, to consider (a) terminology used, (b) presentation of the de-
17 368 prescribing approach and (c) presentation of randomisation. This will inform on-going trial procedures and
18 369 future implementation.

19 370

20 371 #

21 372 This work will adapt a previous decision-analytic model examining the long-term costs and benefits from
22 373 blood pressure lowering treatment³⁹ to include potential harms of treatment. The model will be adjusted
23 374 for the effects of blood pressure lowering on cardiovascular disease risk, costs and quality-adjusted-life
24 375 years (QALYs) to match the older population involved in this work. Costs of the therapies prescribed, side-
25 376 effects and acute and long term costs of cardiovascular events will be obtained within the trial and from
26 377 the literature. Quality of life on each treatment strategy will be obtained from the trial data using EQ-5D-5L,
27 378 and previous studies will inform utility values for cardiovascular disease health states and the impact of
28 379 side effects. The model will determine the cost per additional QALY gained of the medication reduction
29 380 intervention versus usual care and analyses will be conducted from a health and social services perspective.
30 381 The model will be run with a lifetime perspective, with costs and benefits discounted at a rate of 3.5%. A
31 382 value of information analysis will assess whether a further trial would be appropriate to reduce decision
32 383 uncertainty, and identify those parameters where more precise estimates would be most valuable and
33 384 should therefore be chosen as outcomes for such a trial.

34 385

35 386

36 387 This research involves older participants, some of whom may be considered vulnerable. Great care will be
37 388 taken to ensure all potential participants have the trial clearly explained, and are given sufficient time to
38 389 decide whether to give informed consent. This will include provision of simplified, participant information
39 390 sheets with large fonts, video infographics to explain the study and extended GP consultation periods for
40 391 explaining the study and taking informed consent. The protocol, informed consent form, participant
41 392 information sheet and all other participant facing material have been approved by the Research Ethics
42 393 Committee (South Central - Oxford A; ref 16/SC/0628), Medicines and Healthcare products Regulatory
43 394 Agency (ref 21584/0371/001-0001), host institution(s) and Health Research Authority. The study sponsor
44 395 reviewed and ensured all indemnity and insurance requirements for the trial were in place prior to the start
45 396 of recruitment.

1 397 All research outputs from this work will be published in peer-reviewed journals, presented at scientific
2 398 conferences and lay and social media (e.g. Twitter, blogs). 'Patient friendly' study summary documents and
3 399 infographics will be made available to all participants at the end of the trial via the study website.
4 400

5 401 *Current trial status*

6 402 The trial commenced recruitment on 10th April 2017 and is estimated to continue recruitment until
7 403 September 2018.
8 404

9 405 +

10 406 Current guidelines in the UK suggest that doctors should ensure that patients are fully informed of the
11 407 benefits and risks of their prescribed medications and where appropriate, discuss the potential for
12 408 medication withdrawal in frail individuals with multi-morbidity.⁴⁰ This is difficult given consultation time
13 409 constraints and fear that de-prescribing might result in harm.⁴¹ This is compounded by conflicting and
14 410 inconclusive evidence about the benefits and harms of treatment, and a lack of evidence about what will
15 411 happen if these treatments are reduced.
16 412

17 413 The ECSTATIC trial enrolled 1,067 younger participants aged 40-70 years, taking antihypertensives for
18 414 primary prevention of cardiovascular disease.¹⁸ The trial demonstrated that only 27% of participants were
19 415 able to maintain medication reduction throughout follow-up and at 3 months, systolic blood pressure was
20 416 on average 6 mmHg higher in the de-prescribing group. At 2 year follow-up, the risk of uncontrolled blood
21 417 pressure was significantly higher in those patients attempting to de-prescribe. Unlike the present study, the
22 418 medication reduction algorithm used did not encourage reintroduction of therapy if blood pressure was
23 419 persistently raised.
24 420

25 421 The DANTE study¹⁶ examined the effect of complete antihypertensive medication discontinuation in 385
26 422 patients over the age of 75 years and with mild cognitive deficits. After 16 weeks of follow-up, they
27 423 observed a 7/3 mmHg increase in blood pressure but no difference in overall cognition compound score or
28 424 quality of life between groups. A study by Van der Wardt and colleagues¹⁹ examined the feasibility trial
29 425 reducing antihypertensives in patients with dementia, but was only able to recruit 9 participants for the
30 426 withdrawal programme (1% recruitment rate) and a larger trial was deemed unfeasible. Similarly, the
31 427 OPTIMED trial⁴² demonstrated in 95 participants that a broader de-prescribing approach is achievable in
32 428 patients living in nursing homes, but was unable to examine the effect on clinical outcomes due to
33 429 recruitment issues resulting on only 38% of the planned sample size being enrolled.
34 430

35 431 The OPTiMISE trial will target frail individuals with polypharmacy and co-morbidity, and aim to establish
36 432 whether a strategy of antihypertensive medication reduction is safe and acceptable to older patients. The
37 433 findings of this trial will support better patient-centred management plans for the prevention of
38 434 cardiovascular disease in older individuals and inform future de-prescribing trials in primary care.
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 435 . %

2 436 The authors acknowledge the support of the Primary Care Clinical Trials Unit, staff from the NIHR CRNs
3 437 including Thames Valley and South Midlands, Cambridge, Southampton, West Midlands (Central and South)
4 438 and West of England, and Lucy Curtin for administrative support. Margaret Ogden and Anita Higham serve
5 439 as patient representatives for the trial steering committee. Additional members of the trial steering
6 440 committee are Prof Tom Robinson (chair), Prof Rod Taylor and Dr Peter Bower. Members of the data
7 441 monitoring committee are Prof John Gladman (chair), Prof Una Martin and Dr Martyn Lewis. The sponsor
8 442 and funder had no role in the study design, writing of the paper; or the decision to submit this protocol for
9 443 publication, which was made jointly by the authors who have all approved the final manuscript. Finally, this
10 444 work would not be possible without the support of the participating practices and participants.
11
12
13
14

15 445

16 446 /

17 447 This work receives joint funding from the National Institute for Health Research (NIHR) Oxford
18 448 Collaboration for Leadership in Applied Health Research and Care (CLAHRC) at Oxford Health NHS
19 449 Foundation Trust (ref: P2-501) and the NIHR School for Primary Care Research (SPCR; ref 335). JS and
20 450 RJMcM have been funded by an NIHR Professorship (NIHR-RP-R2-12-015). FDRH acknowledges part
21 451 support from the NIHR SPCR, the NIHR CLAHRC Oxford, and the NIHR Oxford Biomedical Research Centre
22 452 (BRC). CH receives support from the NIHR SPCR and NIHR Oxford BRC. The views and opinions expressed
23 453 are those of the authors and do not necessarily reflect those of the NHS, NIHR, or the Department of
24 454 Health.
25
26
27

28 455

29 456

30 457 The authors declare no conflicts of interest.

31 458

32 459 0 #

33 460 JS conceived, designed and secured funding for the study with JBu, ML, JBe, GF, CH, FDRH, SJ, PL, JM, EO,
34 461 RP, MW, LMY and RJMcM. JS wrote the first draft. AN, JMo and LMY provided the sample size calculations
35 462 and statistical analysis section. JBu provided the qualitative section. SJ provided the health economic
36 463 section. All authors reviewed and edited the manuscript. ET is the trial manager. JS and RJMcM are co-chief
37 464 investigators and will act as guarantors for this work.
38
39

40 465

41 466 +

42 467 Data sharing requests will be considered by the corresponding author.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2 468 1
3 469
4 470 1. Office for National Statistics. Mid-year populations estimates: Aging, fastest increase in the 'oldest old'.
5 471 <http://www.ons.gov.uk>, 2010.
6
7 472 2. Barnett K, Mercer SW, Norbury M, et al. Epidemiology of multimorbidity and implications for health care,
8 473 research, and medical education: a cross-sectional study. *Lancet* 2012;380(9836):37-43. doi:
9 474 10.1016/s0140-6736(12)60240-2 [published Online First: 2012/05/15]
10
11 475 3. Violan C, Foguet-Boreu Q, Roso-Llorach A, et al. Burden of multimorbidity, socioeconomic status and use
12 476 of health services across stages of life in urban areas: a cross-sectional study. *BMC public health*
13 477 2014;14:530. doi: 10.1186/1471-2458-14-530 [published Online First: 2014/06/03]
14
15 478 4. Sheppard JP, Singh S, Fletcher K, et al. Impact of age and sex on primary preventive treatment for
16 479 cardiovascular disease in the West Midlands, UK: cross sectional study. *BMJ (Clinical research ed)*
17 480 2012;345:e4535. doi: 10.1136/bmj.e4535 [published Online First: 2012/07/14]
18
19 481 5. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older.
20 482 *The New England journal of medicine* 2008;358(18):1887-98. doi: 10.1056/NEJMoa0801369 [published
21 483 Online First: 2008/04/02]
22
23 484 6. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *The New England journal of*
24 485 *medicine* 2015 doi: 10.1056/NEJMoa1511939 [published Online First: 2015/11/10]
25
26 486 7. McKee M, Britton A, Black N, et al. Interpreting the evidence: choosing between randomised and non-
27 487 randomised studies. *BMJ (Clinical research ed)* 1999;319(7205):312-5.
28
29 488 8. van Deudekom FJ, Postmus I, van der Ham DJ, et al. External validity of randomized controlled trials in
30 489 older adults, a systematic review. *PloS one* 2017;12(3):e0174053. doi: 10.1371/journal.pone.0174053
31 490 [published Online First: 2017/03/28]
32
33 491 9. Bejan-Angoulvant T, Saadatian-Elahi M, Wright JM, et al. Treatment of hypertension in patients 80 years
34 492 and older: the lower the better? A meta-analysis of randomized controlled trials. *Journal of hypertension*
35 493 2010;28(7):1366-72. doi: 10.1097/HJH.0b013e328339f9c5 [published Online First: 2010/06/25]
36
37 494 10. Benetos A, Labat C, Rossignol P, et al. Treatment With Multiple Blood Pressure Medications, Achieved
38 495 Blood Pressure, and Mortality in Older Nursing Home Residents: The PARTAGE Study. *JAMA internal*
39 496 *medicine* 2015 doi: 10.1001/jamainternmed.2014.8012 [published Online First: 2015/02/17]
40
41 497 11. Tinetti ME, Han L, Lee DS, et al. Antihypertensive medications and serious fall injuries in a nationally
42 498 representative sample of older adults. *JAMA internal medicine* 2014;174(4):588-95. doi:
43 499 10.1001/jamainternmed.2013.14764 [published Online First: 2014/02/26]
44
45 500 12. Fried TR, Tinetti ME, Towle V, et al. Effects of benefits and harms on older persons' willingness to take
46 501 medication for primary cardiovascular prevention. *Archives of internal medicine* 2011;171(10):923-8. doi:
47 502 10.1001/archinternmed.2011.32 [published Online First: 2011/03/02]
48
49 503 13. Schuling J, Gebben H, Veehof LJ, et al. Deprescribing medication in very elderly patients with
50 504 multimorbidity: the view of Dutch GPs. A qualitative study. *BMC family practice* 2012;13:56. doi:
51 505 10.1186/1471-2296-13-56 [published Online First: 2012/06/16]
52
53 506 14. Scott IA, Anderson K, Freeman CR, et al. First do no harm: a real need to deprescribe in older patients.
54 507 *The Medical journal of Australia* 2014;201(7):390-2. [published Online First: 2014/10/09]
55
56
57
58
59
60

- 1
2 508 15. Iyer S, Naganathan V, McLachlan AJ, et al. Medication withdrawal trials in people aged 65 years and
3 509 older: a systematic review. *Drugs & aging* 2008;25(12):1021-31. doi: 10.2165/0002512-200825120-00004
4 510 [published Online First: 2008/11/22]
- 5
6 511 16. Moonen JE, Foster-Dingley JC, de Ruijter W, et al. Effect of Discontinuation of Antihypertensive
7 512 Treatment in Elderly People on Cognitive Functioning--the DANTE Study Leiden: A Randomized Clinical Trial.
8 513 *JAMA internal medicine* 2015;175(10):1622-30. doi: 10.1001/jamainternmed.2015.4103 [published Online
9 514 First: 2015/08/25]
- 10
11 515 17. van der Wardt V, Harrison JK, Welsh T, et al. Withdrawal of antihypertensive medication: a systematic
12 516 review. *Journal of hypertension* 2017;35(9):1742-49. doi: 10.1097/hjh.0000000000001405 [published
13 517 Online First: 2017/05/10]
- 14
15 518 18. Luymes CH, Poortvliet RKE, van Geloven N, et al. Deprescribing preventive cardiovascular medication in
16 519 patients with predicted low cardiovascular disease risk in general practice - the ECSTATIC study: a cluster
17 520 randomised non-inferiority trial. *BMC medicine* 2018;16(1):5. doi: 10.1186/s12916-017-0988-0 [published
18 521 Online First: 2018/01/13]
- 19
20 522 19. van der Wardt V, Burton JK, Conroy S, et al. Withdrawal of antihypertensive therapy in people with
21 523 dementia: feasibility study. *Pilot and feasibility studies* 2018;4:29. doi: 10.1186/s40814-017-0221-0
22 524 [published Online First: 2018/01/18]
- 23
24 525 20. Nelson MR, Reid CM, Krum H, et al. Predictors of normotension on withdrawal of antihypertensive
25 526 drugs in elderly patients: prospective study in second Australian national blood pressure study cohort. *BMJ*
26 527 (*Clinical research ed*) 2002;325(7368):815. [published Online First: 2002/10/12]
- 27
28 528 21. Nelson MR, Reid CM, Krum H, et al. Short-term predictors of maintenance of normotension after
29 529 withdrawal of antihypertensive drugs in the second Australian National Blood Pressure Study (ANBP2).
30 530 *American journal of hypertension* 2003;16(1):39-45. [published Online First: 2003/01/09]
- 31
32 531 22. Clegg A, Bates C, Young J, et al. Development and validation of an electronic frailty index using routine
33 532 primary care electronic health record data. *Age and ageing* 2016;45(3):353-60. doi: 10.1093/ageing/afw039
34 533 [published Online First: 2016/03/06]
- 35
36 534 23. National Clinical Guideline C. National Institute for Health and Clinical Excellence Guidance CG127.
37 535 Hypertension: The Clinical Management of Primary Hypertension in Adults: Update of Clinical Guidelines 18
38 536 and 34. London: Royal College of Physicians (UK) 2011.
- 39
40 537 24. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version
41 538 of EQ-5D (EQ-5D-5L). *Quality of life research : an international journal of quality of life aspects of treatment,*
42 539 *care and rehabilitation* 2011;20(10):1727-36. doi: 10.1007/s11136-011-9903-x [published Online First:
43 540 2011/04/12]
- 44
45 541 25. Sulter G, Steen C, De Keyser J. Use of the Barthel index and modified Rankin scale in acute stroke trials.
46 542 *Stroke; a journal of cerebral circulation* 1999;30(8):1538-41. [published Online First: 1999/08/06]
- 47
48 543 26. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle
49 544 aged African Americans. *The journal of nutrition, health & aging* 2012;16(7):601-8. [published Online First:
50 545 2012/07/28]
- 51
52 546 27. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people.
53 547 *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*
54 548 2005;173(5):489-95. doi: 10.1503/cmaj.050051 [published Online First: 2005/09/01]

- 1
2 549 28. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief
3 550 screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society* 2005;53(4):695-9.
4 551 doi: 10.1111/j.1532-5415.2005.53221.x [published Online First: 2005/04/09]
- 5
6 552 29. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to
7 553 treatment in chronic physical illness. *Journal of psychosomatic research* 1999;47(6):555-67. [published
8 554 Online First: 2000/02/08]
- 9
10 555 30. Mattu GS, Heran BS, Wright JM. Overall accuracy of the BpTRU--an automated electronic blood
11 556 pressure device. *Blood pressure monitoring* 2004;9(1):47-52. [published Online First: 2004/03/17]
- 12
13 557 31. Lahrmann H, Cortelli P, Hilz M, et al. EFNS guidelines on the diagnosis and management of orthostatic
14 558 hypotension. *European journal of neurology* 2006;13(9):930-6. doi: 10.1111/j.1468-1331.2006.01512.x
15 559 [published Online First: 2006/08/26]
- 16
17 560 32. Gallagher P, Ryan C, Byrne S, et al. STOPP (Screening Tool of Older Person's Prescriptions) and START
18 561 (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *International journal of clinical
19 562 pharmacology and therapeutics* 2008;46(2):72-83. [published Online First: 2008/01/26]
- 20
21 563 33. McManus RJ, Mant J, Bray EP, et al. Telemonitoring and self-management in the control of
22 564 hypertension (TASMINH2): a randomised controlled trial. *Lancet* 2010;376(9736):163-72. doi:
23 565 10.1016/s0140-6736(10)60964-6 [published Online First: 2010/07/14]
- 24
25 566 34. McManus RJ, Mant J, Haque MS, et al. Effect of self-monitoring and medication self-titration on systolic
26 567 blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized
27 568 clinical trial. *Jama* 2014;312(8):799-808. doi: 10.1001/jama.2014.10057 [published Online First:
28 569 2014/08/27]
- 29
30 570 35. Cuspidi C, Meani S, Lonati L, et al. Prevalence of home blood pressure measurement among selected
31 571 hypertensive patients: results of a multicenter survey from six hospital outpatient hypertension clinics in
32 572 Italy. *Blood pressure* 2005;14(4):251-6. doi: 10.1080/08037050500210765 [published Online First:
33 573 2005/08/30]
- 34
35 574 36. Tucker KL, Sheppard JP, Stevens R, et al. Self-monitoring of blood pressure in hypertension: A
36 575 systematic review and individual patient data meta-analysis. *PLoS medicine* 2017;14(9):e1002389. doi:
37 576 10.1371/journal.pmed.1002389 [published Online First: 2017/09/20]
- 38
39 577 37. Walker E, Nowacki AS. Understanding equivalence and noninferiority testing. *Journal of general internal
40 578 medicine* 2011;26(2):192-6. doi: 10.1007/s11606-010-1513-8 [published Online First: 2010/09/22]
- 41
42 579 38. Nathan A, Goodyer L, Lovejoy A, et al. 'Brown bag' medication reviews as a means of optimizing
43 580 patients' use of medication and of identifying potential clinical problems. *Family practice* 1999;16(3):278-
44 581 82. [published Online First: 1999/08/10]
- 45
46 582 39. Kaambwa B, Bryan S, Jowett S, et al. Telemonitoring and self-management in the control of
47 583 hypertension (TASMINH2): a cost-effectiveness analysis. *European journal of preventive cardiology*
48 584 2014;21(12):1517-30. doi: 10.1177/2047487313501886 [published Online First: 2013/08/31]
- 49
50
51 585 40. National Guideline Centre. National Institute for Health and Care Excellence: Clinical Guidelines.
52 586 Multimorbidity: Assessment, Prioritisation and Management of Care for People with Commonly Occurring
53 587 Multimorbidity [NICE Guideline 56]. London: National Institute for Health and Care Excellence (UK)
- 54
55 588 Copyright (c) National Institute for Health and Care Excellence, 2016. 2016.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

589 41. Palagyi A, Keay L, Harper J, et al. Barricades and brickwalls--a qualitative study exploring perceptions of
590 medication use and deprescribing in long-term care. *BMC geriatrics* 2016;16:15. doi: 10.1186/s12877-016-
591 0181-x [published Online First: 2016/01/16]

592 42. Potter K, Flicker L, Page A, et al. Deprescribing in Frail Older People: A Randomised Controlled Trial. *PloS*
593 *one* 2016;11(3):e0149984. doi: 10.1371/journal.pone.0149984 [published Online First: 2016/03/05]

594

For peer review only

1
2 595 /
3 596
4 597 / &' Trial flow diagram

5 598
6 599 *Monitoring of blood pressure at home will be encouraged but those not willing or able will still be
7 600 included in the trial. All participants will be asked to attend a safety monitoring visit with their GP/nurse
8 601 four weeks after baseline.

10 602 GP = General practitioner; BP = Blood pressure; HDL = High density lipoprotein; ICD = International
11 603 Statistical Classification of Diseases and Related Health Problems; CVD = Cardiovascular disease; eGFR =
12 604 estimated Glomerular Filtration Rate (eGFR); MARS = Medication Adherence Rating Scale; MOCA =
13 605 Montreal Cognitive Assessment

16
17 606 /)' Medication reduction algorithm

19 607
20 608 Withdraw the one of the following medications if any of the ensuing contraindications are identified:

- 21 609 - Thiazide diuretic with a history of gout (may exacerbate gout).
- 22 610 - Beta-blocker in combination with verapamil (risk of symptomatic heart block).
- 23 611 - Non-cardioselective beta-blocker with chronic obstructive pulmonary disease (risk of
- 24 612 bronchospasm).
- 25 613 - Calcium channel blockers with chronic constipation (may exacerbate constipation).
- 26 614 - Use of diltiazem or verapamil with NYHA Class III or IV heart failure (may worsen heart failure).

29
30 615 / 2' Post medication reduction monitoring flow chart

32 616 Note: The full effects of most oral antihypertensives can last for up to 4-6 weeks. Frequent monitoring in
33 617 the initial 4 weeks after drug withdrawal is thus not required unless BP levels are extreme or there are
34 618 other clinical concerns (see above). Where systolic/diastolic BP values fall into different categories, consider
35 619 the higher value. BP should be taken as the averaged second and third measurements using a validated
36 620 monitor. Standard clinical care/monitoring should align with NICE recommendations.²³

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

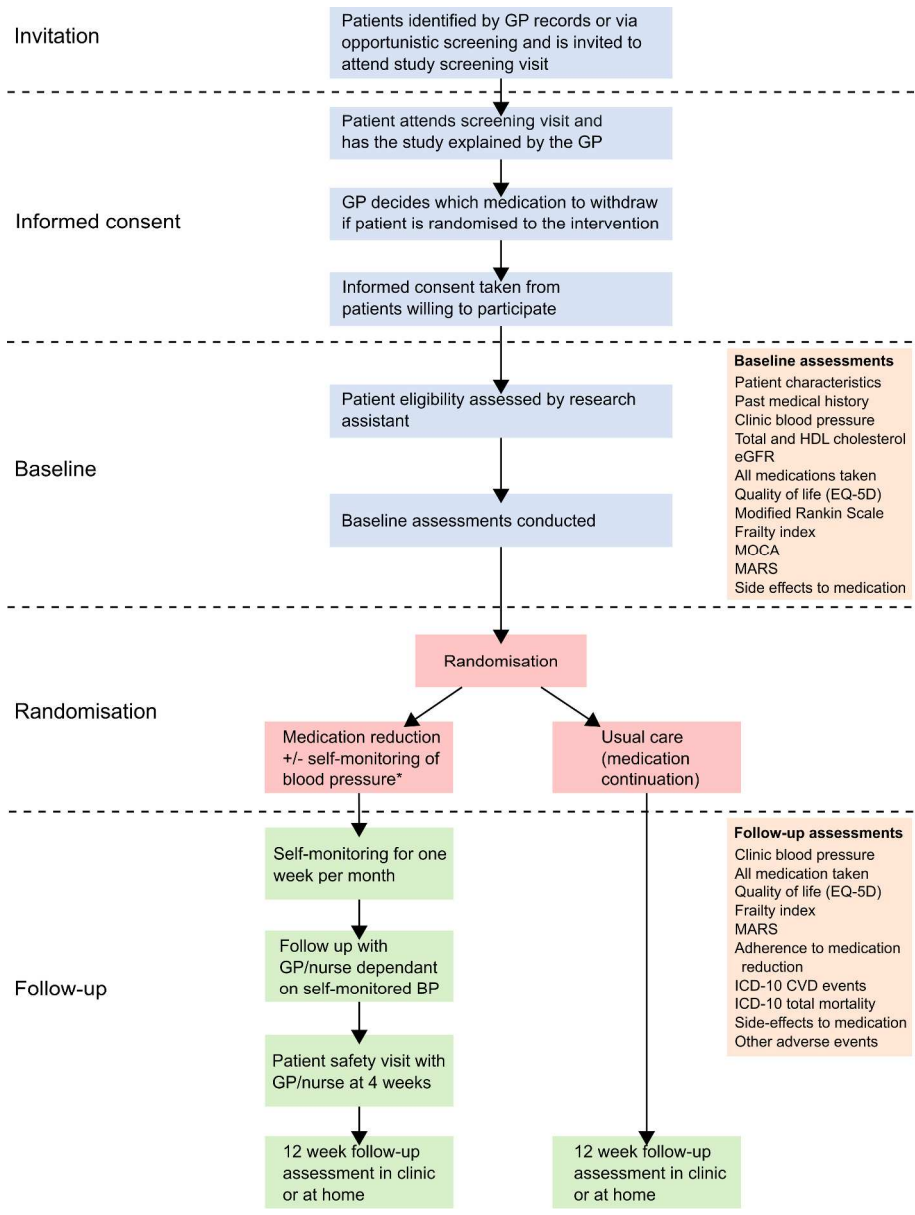


Figure 1

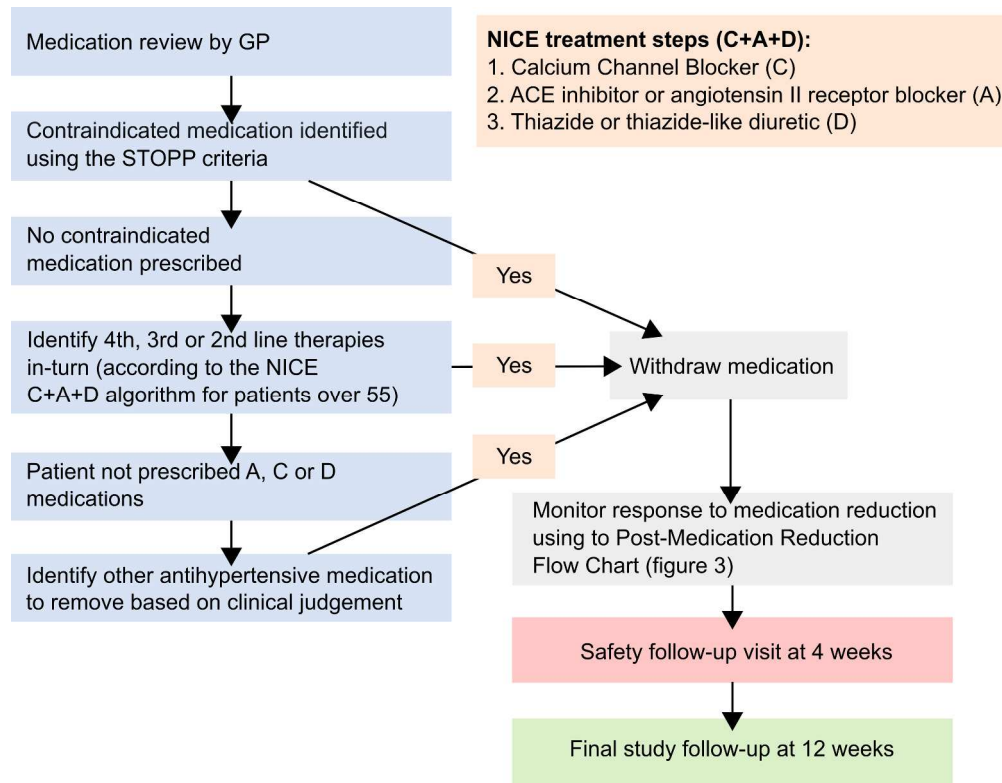


Figure 2

ew only

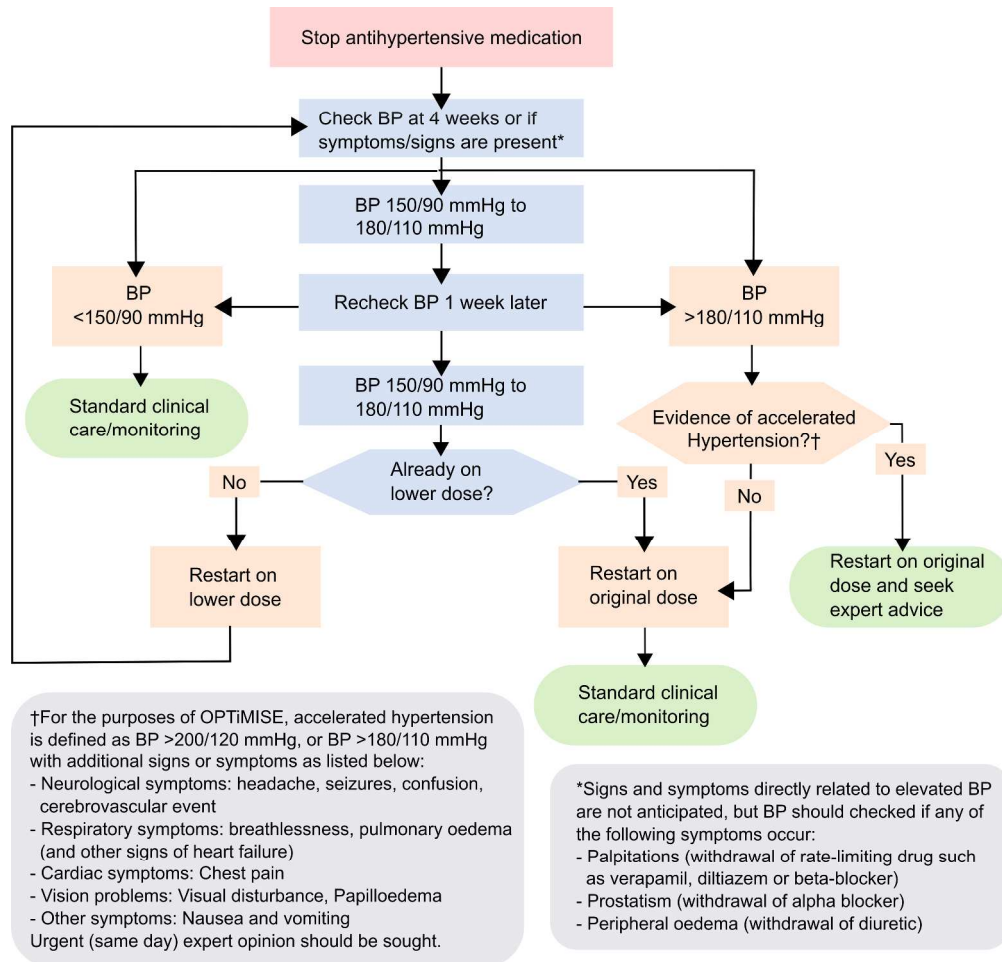


Figure 3



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Page in protocol |
|---|---------|--|------------------|
| Administrative information | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | n/a |
| Protocol version | 3 | Date and version identifier | n/a |
| Funding | 4 | Sources and types of financial, material, and other support | 12 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1, 12 |
| | 5b | Name and contact information for the trial sponsor | 1 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 12 |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 12 |
| Introduction | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 3 |
| | 6b | Explanation for choice of comparators | 3 |
| Objectives | 7 | Specific objectives or hypotheses | 3-4 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 4 |
| Methods: Participants, interventions, and outcomes | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 4 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will | 4, table 1 |

| | | | |
|---|-----|--|----------|
| | | perform the interventions (eg, surgeons, psychotherapists) | |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 5 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | Figure 3 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | 6-7 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 7 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 4-5 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Figure 1 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 8 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 5 |
| Methods: Assignment of interventions (for controlled trials) | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 6 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 6 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 6 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 6 |

| | | | |
|---|-----|--|-----|
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 6 |
| Methods: Data collection, management, and analysis | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 5-7 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 7 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 6 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 8 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 8 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 8 |
| Methods: Monitoring | | | |

