Trial Title: Telemonitoring and/or self-monitoring of blood pressure in hypertension: A randomised controlled trial in primary care

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Chief Investigator (CI): Professor Richard McManus,
Department of Primary Care Health Sciences, University of Oxford

2nd floor, New Radcliffe House, Radcliffe Observatory Quarter,
Woodstock Road, Oxford, OX2 6GG

Tel: + 44 (0)1865 617834

Fax: + 44 (0)1865 289287

Email: richard.mcmanus@phc.ox.ac.uk

Investigators: Dr James Hodgkinson, Dr Sabrina Grant, Siobhan Milner, Dr Sue Jowett, Dr Una Martin, Prof Sheila Greenfield (University of Birmingham)

Dr Rafael Perera, Dr Ly Mee Yu, Prof Carl Heneghan, Dr Claire Schwartz, Dr Alison Ward, Ben Fletcher, Prof Andrew Farmer, Professor Richard Hobbs (University of Oxford)

Prof Jonathan Mant (University of Cambridge)

Sponsor: University of Oxford

Joint Research Office
Block 60
Churchill Hospital
Old Road
Headington
Oxford OX3 7LE

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Chief Investigator Signature: 26/1/2015

Prof Richard McManus Date

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Potential conflicts of interest: Blood Pressure Monitors for this trial are supplied by Omron

Confidentiality Statement

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1. SYNOPSIS

Trial Title	**Telemonitoring and/or self-monitoring of blood pressure in hypertension: A randomised controlled trial in primary care**	
Internal ref. no. (or short title)	TASMINH 4	
Trial Design	Pragmatic unblinded individual patient randomised controlled trial – three arm parallel group	
Trial Participants	Patients with hypertension	
Planned Sample Size	1110	
Treatment duration	12 months	
Follow up duration	12 months for each patient with longer term vital status follow up	
Planned Trial Period	3 years (6m set up, 1 year of baseline clinics to recruit sufficient numbers of patients plus 1 year of the intervention itself, 6m write up)	
	Objectives	Outcome Measures/Endpoints
Primary	To evaluate the management of hypertension in primary care using self monitored blood pressure, with or without telemonitoring compared to standard care.	Systolic BP (blood pressure) at 12 months (mean of 2nd and 3rd BP readings)
Secondary/tertiary	a) Primary research questions using secondary measures of blood pressure b) Is self-monitoring acceptable to patients and cost-effective? c) Does self-monitoring affect antihypertensive medication adherence? d) Does self-monitoring affect lifestyle factors including smoking, alcohol, diet and exercise? e) Is it possible to use routine General Practice (GP) clinical systems to collect sufficiently robust data for a subsequent trial powered on cardiovascular outcomes?	a) Systolic (6m) and diastolic BP (6 and 12m) b) Costs, health sector resource use, and acceptability c) Medical Adherence Rating Scale (MARS) adherence questionnaires and prescribing data d) Questionnaire data on lifestyle factors e) Comparison between trial outcome data and that from Clinical Practice Research Datalink (CPRD)

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2. ABBREVIATIONS

BP	Blood Pressure
CI	Chief Investigator
CKD	Chronic Kidney Disease
CPRD	Clinical Practice Research Datalink
CRF	Case Report Form
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
GP	General Practitioner
ICER	Incremental Cost-Effectiveness Ratios
ICF	Informed Consent Form
ITT	Intention-to-treat
MARS	Medication Adherence Rating Scale
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NIHR	National Institute for Health Research
PC-CTU	Primary Care Clinical Trials Unit
PCRN	Primary Care Research Network
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
QALY	Quality-Adjusted Life Year
RCGP	Royal College of General Practitioners
REC	Research Ethics Committee
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SM	Self-Monitoring
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TM	Telemonitoring
UC	Usual Care

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3. BACKGROUND AND RATIONALE

Blood pressure (BP) is a key risk factor for cardiovascular disease, the largest cause of morbidity and mortality worldwide.(1) A 10 mmHg reduction in BP is estimated to lead to a 41% reduction in stroke and a 22% reduction in CHD.(2) National and international surveys suggest that despite significant improvements in recent years, BP control within the population remains sub-optimal.(3) Self-monitoring as an intervention has been shown to reduce BP,(4) improve adherence to antihypertensive medication,(5) and reduce primary care consultation rates at no additional cost.(6) The current (2004, updated 2006 & 2011) National Institute for Health and Care Excellence (NICE) guideline states: "the value of routinely using ... home (BP) monitoring devices has not been established: their appropriate use in primary care remains an issue for further research".(7) This trial is part of a programme of work aims to provide such evidence and is aligned with current policy objectives namely "putting patients first, improving healthcare outcomes and improving efficiency".(8)

Importance

Within the National Health Service (NHS), over 13% of the population are currently recorded on hypertension registers, almost 7 million in England alone.(9) Despite this, community surveys suggest significant numbers of people have undiagnosed hypertension, and a significant proportion of those receiving treatment do not have their BP adequately controlled: according to the Health Survey for England 2011, almost two fifths of men and women receiving treatment for hypertension were unsuccessful in reducing their blood pressure to a level below 140/90mmHg, and a further 14% of men and 11% of women were untreated despite having a BP over 140/90mmHg.(10) Whilst this is likely to be an overestimate (BP measured on a single occasion and no account taken of underlying cardiovascular risk), it suggests the numbers of individuals in the population whose BP is sub-optimal is significantly more than the number currently adequately treated. From a European perspective, mean BP in the UK currently ranks amongst the highest (27th/35); and the benefits of a population-wide reduction to levels seen in countries such as Denmark or Spain (which are amongst the lowest) would be mean a 10 mmHg systolic BP reduction.(11)

The current system, relying on clinic based measurement, is not suited to appropriate management of those currently at risk with inadequate treatment. However, self-monitoring of hypertension might be a solution: it is simple, leads to reduced BP and is already practiced by around 30% of hypertensives in the UK. Compared to clinic readings, it provides a better estimate of both underlying BP and BP variability – recently hypothesised to be as important as mean BP in predicting stroke risk – and is better correlated with clinically relevant outcomes such as stroke and coronary heart disease.

Patients with hypertension consult about 4 times per year for BP related issues.(6) Self-monitoring has been shown to significantly reduce this – by around 1 consultation per

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year.(6) It could also alter the content of consultations: measuring BP properly within a consultation takes time and therefore reduces the opportunity for appropriate management. In order for self-monitoring to become practical on a wide scale, it would need to be seamlessly integrated within standard hypertension management.

Need for the research

Factors responsible for suboptimal BP control include those due to patients, physicians and the health system.(12) Patient factors principally comprise adherence to medication and other health behaviours. Self-monitoring has been shown, in a US context, to be important in "activating" a health behavioural approach and seems to be useful in improving adherence: a systematic review including 11 randomised controlled trials of self monitoring that reported measures of treatment adherence found that six showed a statistically significant improvement in adherence.(5;13) Clinical inertia is a key issue, (14) whereby clinicians fail to intensify treatment, despite evidence of inadequate control.

A recent Scottish study found that treatment was not intensified in nearly half (45%) of consultations in which patients had a single BP reading above target, and around a third (36%) with two successive readings above target.(15) System of care is the final key issue in gaining control of BP, and a recent Cochrane review concluded that "an organised system of registration, recall and regular review allied to a vigorous stepped care approach to antihypertensive drug treatment appears the most likely way to improve the control of high BP."(16) However, given the numbers of individuals currently not identified as having raised BP and the inadequate control of many receiving treatment, achieving a comprehensive system within the NHS in the current economic climate is likely to be challenging.

Self-monitoring, by reducing consultation rate whilst improving BP control, has the potential to be a useful intervention. However, despite the prevalence of self- monitoring, it is currently poorly integrated into daily practice with many General Practioners (GPs) unsure how to interpret or utilise such measurements.(17) Due to lack of a strong evidence base, self monitoring is not recommended in current guidelines (NICE 2011) to guide routine management of hypertension in the UK.

Previous and current research

Self-monitoring of BP is associated with reductions of BP and improved control compared to target.(4) However, the only study to compare titration by physicians using self-monitoring with titration using office monitoring was confounded by a lack of differentiation between office and self-monitored target.(18) This study found that self-monitoring was associated with lower intensity treatment and higher BP compared to office measurement. This type of study has never been undertaken in a UK setting using a home target which takes into account the adjustment required for lower BP measurements nor has telemonitoring been compared to self-monitoring alone.(19)

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Key work by our group that underpins this trial includes:

1) Survey of self-monitoring in primary care: a Royal College of General Practitioners (RCGP) Foundation funded study by our group reported a prevalence of self-monitoring of 30% within primary care patients with hypertension.(20) This shows that appreciable numbers of people are now self-monitoring but compared with international surveys (75% self-monitor in Europe and US), there is still a significant opportunity to expand participation. A further survey in 2011-12 has shown an increase of self-monitoring in hypertension to around 40%.[data on file]

2) Targets and self-monitoring in hypertension (TASMINH, 2001-5): our group published the first UK data on the efficacy of self-monitoring in hypertension without telemonitoring) which showed that self-monitoring in practice waiting rooms reduced BP in the short term (6m) but that this was not sustained at 12 months.(6) Consultation rate was reduced and costs were no more than usual care. Key issues were: a) self-monitoring was feasible - 75% monitored as requested over the year and median number of months with monitoring was 11; b) Greater integration into usual care was required (approximately 50% of patients did not share BP data with their GPs despite a year of self-monitoring and being explicitly asked to); c) patients preferred home monitoring to practice based self-monitoring.

3) In 2010 we published the first adequately powered trial of self- management in hypertension (TASMINH2) and have undertaken a new trial testing self- management in high risk populations (TASMIN-SR, submitted for publication).(21) We have shown that self-management results in significantly lower BP compared to usual care in people with poorly controlled hypertension who are willing to self-manage and similarly in a group with previous stroke, coronary heart disease, chronic kidney disease or diabetes.

Subsequent data from Edinburgh (self-monitoring with telemonitoring; follow up for 6m with ambulatory monitoring outcome) (22) and London (self-monitoring after stroke, follow up for 12m with clinic blood pressure) (23) has provided further UK data demonstrating reduction of blood pressure with self-monitoring but issues remain regarding a) the impact and necessity of telemonitoring, b) whether titration by GPs solely on the basis of self-monitoring is effective and c) whether any effects are maintained for at least 12 months.

Integration of self-management into daily practice is likely to be only relevant for a minority of individuals with hypertension hence the need for self-monitoring with GPs directly titrating on this basis and therefore the trial described in this protocol.

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4. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Objectives	Outcome Measures/Endpoints
To evaluate the management of hypertension in primary care using self monitored blood pressure, with or without telemonitoring compared to standard care.	Systolic BP at 12 months (mean of 2nd and 3rd BP readings)
Secondary Objectives Is the effect seen for conventional systolic blood pressure (SBP) consistent for diastolic and does it remain when controlling for habituation to repeated measurement?	Systolic (6m) and diastolic BP (6 and 12m) using mean of 2nd to 6th BP readings (BP-TRU)
Tertiary Objectives a) What is the effect of self-monitoring on adherence, side effects, quality of life, adverse events, lifestyle behaviour and costs?	Measures of **adherence**: both GP adherence to the protocol (by analysis of treatment decisions) and patient adherence with prescribed medication (by adherence questionnaires and electronic prescription data) will be monitored throughout the study. Patients in the intervention group(s) will be monitored for fidelity of the intervention. **Side effects and safety**: a symptom questionnaire will be recorded at 6 & 12 months. Quality of life will be measured using EQ-5D.(24) Adverse events will be recorded. **Lifestyle behaviour**: will be measured using validated questionnaires (detailed in Table 1) for smoking, alcohol, exercise and diet. **Resource use and costs**: Health sector resource use and costs will be recorded at 6 and 12 months and compared between groups.
b) Is it possible to use routine GP clinical systems to collect sufficiently robust data for a subsequent trial powered on cardiovascular outcomes?	Cardiovascular Events and deaths: data concerning cardiovascular events and death will be collected both manually from the clinical record and patient report and automatically using the clinical practice datalink to allow comparison in terms of "test performance" measures. Similar data regarding adherence, blood pressure and

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	other routinely measured data will be collected in both ways.

5. STUDY DESIGN

TASMINH4 is a pragmatic un-blinded individual; patient randomised controlled trial. At least 1110 patients with hypertension recruited from primary care will be randomised into one of the three groups: self-monitoring alone, self-monitoring with telemonitoring, and clinic monitoring (1:1:1). There will be embedded economic and qualitative sub studies.

6. PARTICIPANT IDENTIFICATION

6.1. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the trial.
- Male or Female, aged 35 years or above.
- On practice hypertension register, not already taking more than 3 anti-hypertensive agents and above clinic target BP (i.e. ≥140/90 mmHg) at baseline (mean of 2nd/ 3rd readings)
- Stable dose of current antihypertensive medication for at least four weeks prior to trial entry.
- In the Investigator's opinion, is able and willing to comply with all trial requirements or has a carer able to help sufficiently (e.g. in the case of physical issues with self-monitoring).
- Willing to allow his or her GP to be notified of participation in the trial.

6.2. Exclusion Criteria

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

- BP below target at baseline (i.e. <140/90 mmHg on clinic measurement at baseline visit).
- Already taking more than 3 anti-hypertensive agents.
- Orthostatic hypotension: more than 20mmHg systolic drop after standing for 1 minute.
- Diagnosed atrial fibrillation.
- Unwilling to self-monitor.
- BP managed outside of primary care (including secondary hypertension).

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- Unable to provide consent.
- Dementia or score over 10 on the short orientation memory concentration test (and with no carer support),
- Female participant who is pregnant, lactating or planning pregnancy during the course of the trial.
- The partner or spouse of an individual already randomised in the trial
- Chronic Kidney Disease (CKD) Grade 4 or worse; any grade of CKD with proteinuria.
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial (e.g. terminal illness, house bound and unable to attend baseline and follow up clinics).
- Participants who have participated in another research trial involving an antihypertensive medication in the past 4 weeks.

7. STUDY PROCEDURES

7.1. Recruitment

Practices from the Primary Care Research Network (PCRN) will be recruited to take part in the study in collaboration with the PCRN.

Potentially eligible participants will be identified by trained practice staff searching electronic practice-based registers for people whose last systolic blood pressure was recorded to be >145/90 mmHg. These searches will take place in primary care practices from within each of the recruited national PCRNs. The identified patients will be invited to attend an initial clinic by postal invitation including a covering letter from the practice and a participant information sheet (PIS) from the study team. Patients wishing to take part will be asked to contact the research team directly to arrange their initial study appointment.

Patients not responding to the first invitation will receive one reminder. Those who do not wish to take part will be asked to fill in a short questionnaire detailing their reasons (see flow chart in Appendix A).

7.2. Informed Consent

Patients responding to the initial invitation will be seen at an initial study clinic appointment by members of the research team/ network research facilitators/ suitably qualified healthcare professionals who will take informed consent: the PIS and Informed Consent forms (ICFs) will be presented to the participants detailing the exact nature of the trial; what

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it will involve for the participant; the implications and constraints of the protocol and any risks involved in taking part.

The consent will include participation in the study, permission to inform their GP of their participating, permission for access to medical records (to collect information about medication, medical history, clinical outcomes and resource use) and permission to ascertain clinical outcomes and vital status via remote methods and/or the national register. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial.

Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified, trained and experienced, and have been authorised to do so by the Chief/ Principal Investigator (PI) as per the study delegation log. A copy of the signed ICF will be given to the participant. The original signed form will be retained at the trial site with a copy for the patient and the trial team. The participant must personally sign and date the latest approved version of the ICF before any trial specific procedures are performed.

7.3. Screening and Eligibility Assessment

Patients will be screened for eligibility by researchers (PCRN/ research / practice staff) in bespoke clinics comprising confirmation of age, past medical history, current cardiovascular medication, measurement of blood pressure and exclusion of orthostatic hypotension. Once eligibility is confirmed and informed consent is obtained, the baseline questionnaires will be completed prior to randomisation.

7.4. Randomisation, blinding and code-breaking

Eligible patients who have completed the baseline assessment will be individually randomised (i.e. not at practice level) at the baseline clinic using a web based system with manual Primary Care Clinical Trials Unit (PC-CTU) back up. Randomisation will be stratified by practice and minimization will be used taking into account baseline BP, gender, and BP target (standard hypertension, older hypertension and diabetes). Patients will be randomised to one of three groups: self-monitoring alone, self-monitoring with telemonitoring, and clinic monitoring (1:1:1). The study will not be blinded hence code-breaking will be unnecessary. The randomisation schedule will be developed by the study statistician in collaboration with Oxford PC-CTU.

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7.5. Interventions

a) Self-monitoring

Self-monitored groups: the intervention for self-monitored BP has been determined from a systematic review of the literature plus previous experience in the TASMIN trials plus analysis of observational data on self-monitoring:

Patients in the self-monitoring arms will be asked to monitor their blood pressure twice each morning and evening (i.e. four times in all). Patients will self-monitor for the first week of each month.

A paper record sheet will be used for communication in the self-monitoring alone group. Nurses will follow an algorithm that recommends adjustment of antihypertensive medication on the basis of the number of readings above target: if more than half are above target then the algorithm will recommend an increase as used successfully in our previous work. Patient training will include instructions as to what to do in the presence of a high or low reading.

b) Telemonitoring

As self-monitoring but readings transmitted to a secure centralised database from which GP/ nurse can review the records. Readings will be transmitted by free SMS text message. In the telemonitoring group, a mean blood pressure will be automatically calculated. High or low readings will trigger alerts to patient to contact their surgery for a blood pressure check.

For both intervention groups, management will be led by the GP/nurse practitioner, guided by self-monitored BP. Clinic measurement of BP will be discouraged and any clinic measurements (and actions resulting from this) recorded. NICE recommended targets will be used.

7.6. Control Group

Management for the control group will be usual care guided by office BP measured by the GP/practice nurse without further instruction.

In all cases the GP will be free to prescribe any antihypertensive therapy s/he chooses.

7.7. Data Collection

Patients will be seen at baseline and follow up by the research team/ network staff. They will be seen at baseline, 6 months and 12 months, in their own practices. Data will be collected onto paper questionnaires which will form the trial source data.

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7.7.1. Baseline Assessments

At the initial study clinic appointment, network or study research facilitators or health care professionals from the practice will confirm the diagnosis of hypertension, take BP using a standard method and collect baseline data.

Baseline data will comprise those data described in table 1.

Table 1. Data collection throughout the trial

Baseline only:

1. Demographic questions: including age, race, marital status, occupation, and education
2. Duration of hypertension [from notes]
3. Past medical history [from notes and corroborated by patients]
4. Contraindications to anti-hypertensives
5. Short orientation memory test (25)
6. Height

Baseline and follow-up:

1. New medical history (in last 6/12 months)
2. Blood pressure (sitting plus standing at baseline)
3. Current anti-hypertensive medications including complementary herbal or dietary supplements for BP
4. Weight and waist circumference
5. Symptoms part plus short form of Illness Perception Questionnaire (26)
6. Short-form of the State-Trait Anxiety Inventory (27)
7. EQ-5D 5L (24)
8. BP measurement preference (28) [Baseline and 12m follow up only]
9. Medication Adherence Rating Scale (MARS) Questionnaire (29) [Baseline and 12m follow up only]
10. Beliefs about Medicines Questionnaire (31) [Baseline and 12m follow up only]
11. Stanford Expectations of Treatment Scale (SETS) Items 1-6 (32) [Baseline and 12m follow up only]
12. Lifestyle questions: alcohol (Audit-C [33]), diet (Short Food Frequency Questionnaire [34]), exercise (Godin Leisure-Time Exercise Questionnaire [35]), smoking (Smoking tool kit 36) [Baseline and 12m follow up only]

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7.7.2. Follow up:

Subsequent follow up visits will be at six and twelve months for recording of outcome data. Patients will be followed up by either a network or study research facilitators or health care professionals from the practice at 6 months and 12 months post randomisation to: (see table 1) measure BP in a standardised manner, administer study questionnaires, review the clinical record to monitor prescription use and details of any cardiovascular events, collect data on resource use and costs.

In addition, patients will be flagged for mortality and location at the NHS Central Register. Following final follow up, data will be extracted using Clinical Practice Research Datalink (CPRD) from participating practices in order to validate death, risk factor recording and cardiovascular disease coding. Explicit consent for both activities is included in the consent form.

Side effects and safety: a symptom questionnaire will be recorded at 6 & 12 months. Quality of life will be measured using EQ-5D.(24) Adverse events will be recorded.

7.8. Discontinuation/Withdrawal of Participants from Trial Intervention

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

- Ineligibility (retrospectively in case of having been overlooked at screening)
- An adverse event which results in inability to continue to comply with trial procedures
- Disease progression which results in inability to continue to comply with trial procedures
- Withdrawal of consent
- Loss to follow up

In general an intention-to-treat (ITT) approach will be taken so that even if an intervention is withdrawn or a patient in the control group starts to self-monitor [as recorded at follow up], we will ask all participants to attend all follow-up visits as far as is practicable. Data already collected from patients who withdraw consent for continuation in the trial will be used even if they withdraw. Unless a participant withdraws consent, vital status will be assessed even where an individual has been lost to follow-up (for instance moved away).

The reason for withdrawal will be recorded in the Case Report Form (CRF) where possible.

7.9. Definition of End of Trial

The end of the trial will be the date that the last face to face follow-up data is collected from the last patient. Passive follow-up will continue after the trial has finished through the national register +/- CPRD provided that consent remains in place

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7.10. Length data will be held for:

Data regarding the trial will be held for at least 10 years following publication. In order for CPRD and national register follow up, it will be necessary to hold personal data for at least 10 years following the end of follow up.

7.11. Economic sub study: Is the management of hypertension through self-monitoring cost effective?

The economic evaluation will comprise of a within-trial analysis and model-based analysis to extrapolate beyond the trial results.

a) Trial-based analysis

Research Question: What is the cost-effectiveness of changing care to self-monitoring (with or without telemonitoring) compared with both in trial clinic monitoring and usual care?

Data collection: NHS costs will be determined for health care resource use over the 12 month follow-up period of the trial. Resource use will include primary care consultations (GP and practice nurse visits), secondary care referrals, hospital inpatient stays and antihypertensive medications. Data on trial-specific resources such as consultations, equipment for self-monitoring and telemonitoring and training will also be collected. Unit costs will be derived from published sources.

Analysis: The cost-effectiveness analysis will consider the cost per additional 1 mmHg reduction in SBP from baseline to 12 months. A cost-utility analysis will determine the cost per Quality-Adjusted Life Year (QALY) gained over the same period, using patient responses to the EQ-5D 5L. The results for both outcomes will be expressed in terms of Incremental Cost-Effectiveness Ratios (ICERs). The base case economic evaluation will adopt an NHS perspective. The analysis will also consider all three arms of the trial, comparing self-monitoring with and without telemonitoring to control.

Sensitivity analysis will test the robustness of the results. Key parameters will be varied to determine the impact of changes on results. Non-parametric bootstrapping and probabilistic sensitivity analysis will be undertaken to explore uncertainty in the confidence to be placed on the results of the economic analysis and cost effectiveness acceptability curves presented.

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b) Model-based analysis

Procedure: A Markov model-based analysis will consider long-term cost effectiveness by linking intermediate outcomes (i.e. change in BP) to cardiovascular events, and will consider the BP monitoring options within the trial and usual care. The model will determine the cost per additional QALY gained for alternative monitoring scenarios.

Data from the trial and literature will inform the probability of these events occurring and the risk reduction afforded by the alternative strategies. Attached to each health state will be associated health state utility values in order that QALYs can be calculated. Quality of life on each treatment strategy will be obtained from the trial data on EQ-5D 5L, and previous studies will inform utility values for cardiovascular disease health states. Costs of monitoring and the therapies prescribed in each strategy and acute and long term costs of cardiovascular events will be obtained within the trial and from the literature.

Analysis: The base-case will be conducted from a health and personal social services perspective. The model will be run over patient lifetime, with costs and benefits discounted at a rate of 3.5%. In order to explore uncertainties in the analyses, deterministic sensitivity analysis will test the robustness of the model when varying key model parameters and structural assumptions. Probabilistic sensitivity analysis will be undertaken to incorporate the uncertainty around parameter values and quantify the overall decision uncertainty, and inform whether further research is required.

7.12. Qualitative sub study: Is the management of hypertension by self-monitoring acceptable to patients and professionals?

This study will provide qualitative data regarding the views of patients and professionals as to the acceptability of self-monitoring in the routine management of hypertension.

Research Question: Is self-monitoring of BP an acceptable alternative to office monitoring in the management of hypertension?

Methods: We will seek views of patients and clinicians about the acceptability of using self monitored BP in the routine management of hypertension. Up to 30 patients and 30 clinicians who have taken part in the trial will be interviewed to explore barriers and facilitators to such management both before and after the trial.

Recruitment: Participants will be selected purposively from participating practices to ensure a maximum variety sample which reflects the range of professional and participant characteristics.

Consent: Patients and professionals taking part in the interview substudy will be individually consented. Where a carer wishes to be present they will also be consented. All interviews will be audio recorded with explicit consent for the use of anonymised quotes.

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Interview content: An important focus of the interviews will be on identifying: perceived barriers for both patients and practitioners; where similarities and differences in perception lie; appropriate behaviours and information sharing between patient, practitioner and practice staff necessary to maximise successful management and patient and practitioner satisfaction. Interviews will be recorded and transcribed verbatim.

Analysis: Interviews will be analysed thematically to bring out both 'articulated' data i.e. direct responses to questions on the areas described above as well as 'emergent data' i.e. new information about the joint patient/practitioner partnership which is a central component of successful self-management which emerges from comparison of themes.

8. TRIAL FIDELITY PROCEDURES

8.1. Assessing and assuring compliance with trial interventions

Measures of adherence: both GP adherence to the protocol (by analysis of treatment decisions) and patient adherence with the protocol and patient adherence with prescribed medication (MARS [29,30]) and electronic prescription data will be monitored at follow-up.

Practice Training: Prior to the trial commencing, participating GPs and practice nurses will receive study specific training. Practices will be asked for confirmation of calibration checks of their sphygmomanometers. Patients will be issued with validated electronic sphygmomanometers to use during the study (provided by Omron). In the self-monitoring groups, clinic measurement of BP will be discouraged and any clinic measurements (and actions resulting from this) recorded. This will be done via training and exception reports for the GPs and training for the patients as to what to expect.

8.2. Concomitant Medication

All medication taken by participants, both antihypertensive and other drug classes will be at the discretion of participating practices.

9. SAFETY REPORTING

We do not anticipate that the study methodology should result in any serious adverse events (SAEs) but include this section in case such events are reported so that they can be considered for causal links to the study. Only SAEs that are clinically judged (by GP) as being caused by the trial intervention will be reported to the PC-CTU who will inform the REC that gave favourable opinion. We will not report side effects as stated in the BNF as SAEs. We will collect data regarding admissions to hospital, cardiovascular events and deaths as part of the tertiary objectives and for the health economic analysis. We will routinely review these at

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the steering group and consider whether there is any evidence suggesting a causal link to trial procedures. Previous trials by our group have failed to find any evidence of such a link.

10. STATISTICS AND ANALYSIS

10.1. Description of Statistical Methods

The primary statistical analysis will be on the basis of ITT. That is, after randomisation, participants will be analysed according to their allocated treatment group irrespective of what treatment they actually received. A mixed effect model will analyse the primary outcome utilising data collected at 6 and 12 months from randomisation, adjusting for baseline BP measure and minimisation variables. Similar methods will be used for other continuous outcomes. The two self-monitoring groups will first be compared to the clinic monitoring group. If both of the treatments are found to be more effective than usual care they will be compared to each other. Differences in diastolic BP, other BP measurements, quality of life, adherence and frequency of adverse effects will be investigated using similar methods (secondary and tertiary outcomes).

Sensitivity analyses will be carried out to examine the robustness of the results with different assumptions about departures from randomisation policies, and handling of missing data.

10.2. The Number of Participants

The study requires a total sample of 1110 patients to be recruited with 370 randomised to Usual Care (UC) and 740 randomised to self-monitoring (SM) with or without telemonitoring (TM), comprising 370 in the SM only group and 370 in the SM+TM group. This is based on a common standard deviation of 17mmHg and a three way pairwise comparison (SM vs SM+, SM vs UC, SM+ vs UC), at least 367 participants per group (allowing for 15% attrition) would allow us to detect a 5mmHg difference between groups (i.e. standardised effect size = 0.3) with 90% power and an adjusted alpha of 0.017 (to account for the three way comparison).

Previous experience suggests that around 120-150 practices will be required to recruit a sample of this size: assuming an average list size of 7000, with a prevalence of hypertension of 13%, of whom approximately 16% will respond to a trial invitation and 40% of these will be eligible. This corresponds to around 7-10 patients per practice.

10.3. The Level of Statistical Significance

Level of significance will be done at 5% two-sided significant level. P-values will be adjusted for any multiple comparisons in order to maintain an overall type I error rate of 5%.

10.4. Criteria for the Termination of the Trial

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The trial is of a method of management rather than a medicinal product and it is not anticipated that the trial will be terminated unless on the advice of the Data Monitoring Committee (DMC) in the case of a series of Suspected Unexpected Serious Adverse Reactions (SUSARs). No interim analysis is planned.

10.5. Procedure for Accounting for Missing and Spurious Data.

Missing data: Missing data will be reported with reasons given where available and the missing data pattern will be examined. We will explore the mechanism of missing data, though the mixed effects model implicitly accounts for data missing at random. The need for a sensitivity analysis taking into account missing data using multiple imputation will be considered.

Spurious data: Spurious data will be assessed using standard editing criteria.

10.6. Inclusion in Analysis

All data will be included in the analysis as far as possible to allow full ITT analysis, though there will inevitably be the problem of missing data due to withdrawal, loss to follow-up, or non-response questionnaire items.

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

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

11. DATA MANAGEMENT

11.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations.

11.2. Data Recording and Record Keeping

The clinical database built and managed by the PC-CTU will hold and allow data management of all data points required to conduct the final analysis. The clinical database will be built on an externally validated secure web-based platform allowing for data tracking by use of date stamped audit logs. Within this database participants will be identified only by a unique study ID to offer patient confidentiality and protect against bias.

The data collected on paper CRFs will be held securely in a locked cabinet in a locked room in a restricted access building.

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Patient identifiers will only be collected if patient consent is given and it is absolutely necessary to facilitate the delivery of the study. For example in the case where a follow-up phone call is required to a patient, access to this data will be strictly on a need to know basis. The identifiers will be held separately from the CRFs collecting clinical data. The data will be anonymised as soon as possible once it is no longer needed for the study procedures to be carried out. This process will be detailed in a trial specific procedure and the study specific data management plan.

A clinical data manager will be assigned to the study supervised by Oxford PC-CTU's Senior Clinical Data Specialist and PC-CTU Standard Operating Procedures (SOPs) will be followed.

12. QUALITY ASSURANCE PROCEDURES

In line with standard PC-CTU procedures, a study specific risk assessment will be carried. The risk assessment will identify any trial specific risks to participants' safety or well-being or that may impact on the integrity or reliability of the resulting data. The risk assessment will detail how all identified risk will be minimised and inform a trial specific monitoring plan.

The Chief Investigator (CI) will ensure that the trial is conducted at all times in line with the currently approved version of the protocol, PC-CTU SOPs and all applicable regulations.

The programme steering committee will act as the trial steering committee and will be advised by an independent DMC.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

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

13.2. Guidelines for Good Clinical Practice (GCP)

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with GCP.

13.3. Approvals

The protocol, ICF, PIS and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.

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

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13.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

13.5. Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

Confidentiality of potential participants in the programme will be maintained by making the initial searches of the practice computer systems and subsequent study invitations the responsibility of the practice. All data will be kept in locked filing cabinets and/or in password protected databases.

13.6. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate. Patients in the self-monitoring arm will be provided during the trial with validated BP monitoring equipment, and those in the additional telemonitoring arm will have access to a free texting service for the same period.

13.7. Other Ethical Considerations

The main ethical issues associated with this research are confidentiality and informed consent (considered above), and ensuring that participation in the research does not lead to inferior care.

In randomising patients for research, the concern for patients is that those in the control arms of each study might be receiving inferior care to those in the intervention arms or vice versa. In the case of each study, true doubt in terms of the most appropriate management, i.e. "equipoise," exists making it appropriate to investigate the research questions. Furthermore, all trial participants will have more regular monitoring than they will be used to and as such are likely to benefit from the "Hawthorne effect" of taking part in research. We will exclude from the study people for whom testing a particular intervention is inappropriate for example, where it has already been decided that intensive BP lowering is best for an individual.

14. FINANCE AND INSURANCE

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14.1. Funding

The trial is funded via a Programme grant: RP PG 1209 10051

14.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). Clinical treatment in terms of antihypertensive treatment etc will be indemnified via General Practitioners' standard clinical indemnity arrangements.

15. PUBLICATION POLICY

All co-investigators will be eligible to be authors, and will be invited to comment on drafts of papers to be submitted for publication.

Trial participants will be asked if they wish trial results to be disseminated to them and if so, we will provide a copy of published papers to them.

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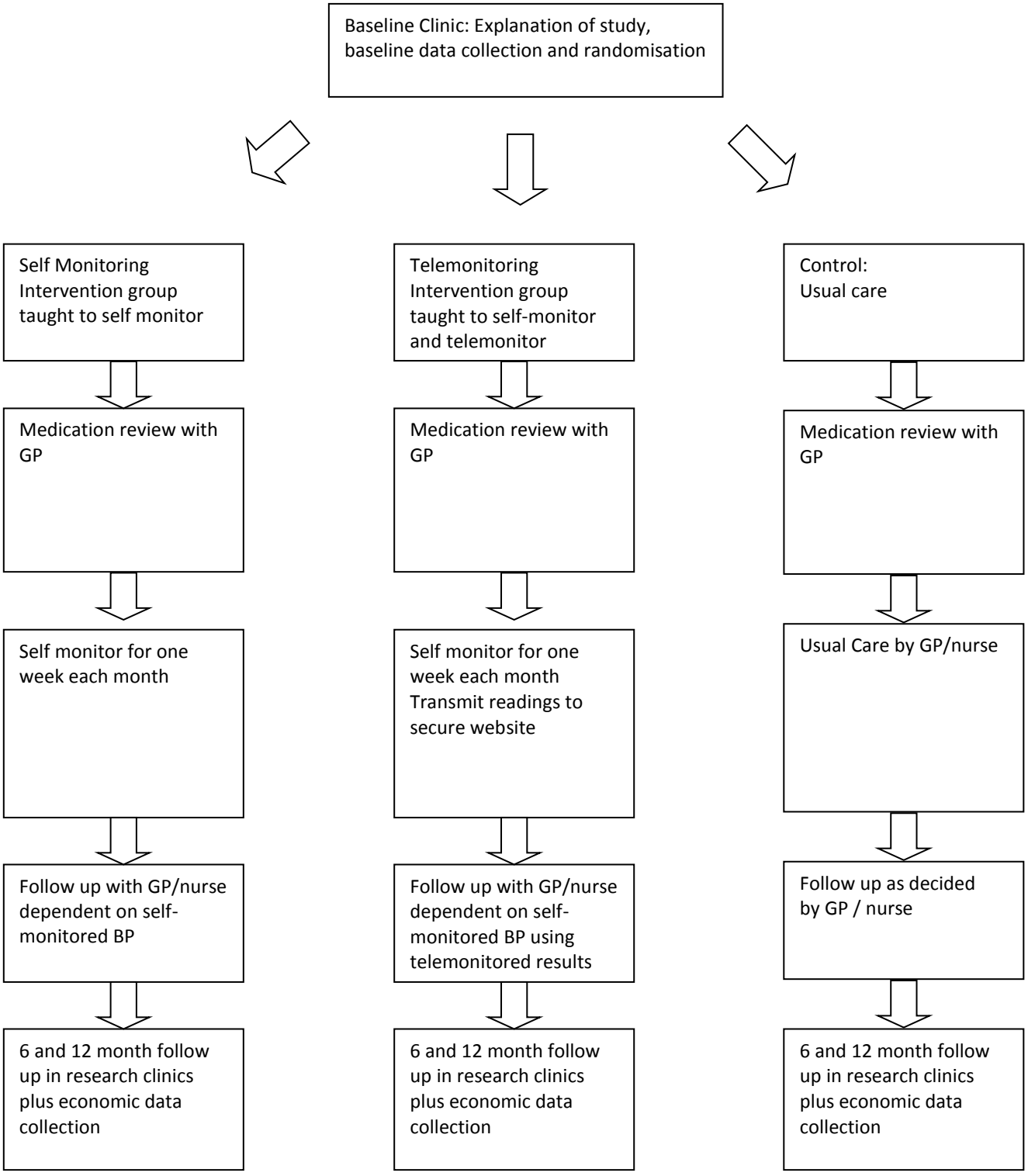
17. APPENDIX A: STUDY FLOW CHART

Flow through the trial:



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18. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures	**Screening/baseline**	**Follow up 1**	**Final Follow up**
Informed consent	x		
Eligibility assessment	x		
Randomisation	x		
Demographics	x		
Medical history	x	x	x
Concomitant medications	x	x	x
Adherence	x	x	x
Blood pressure	x	x	x
Height	x		
Weight	x	x	x
Trial specific questionnaires	x	x	x
Adverse event assessments	x	x	x

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19. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

List details of all protocol amendments here whenever a new version of the protocol is produced. This is not necessary prior to initial REC submission.

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