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Individual patient data meta-analysis of self-monitoring of blood pressure (BP-SMART) Protocol paper

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Individual patient data meta-analysis of self-monitoring of blood pressure (BP-SMART) Protocol paper

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Abstract

Introduction:

Self-monitoring of blood pressure is effective in reducing blood pressure in hypertension. However previous meta-analyses have shown a considerable amount of heterogeneity between studies, only part of which can be accounted for by meta-regression. This may be due to differences in design, recruited populations, intervention components, or results among patient sub-groups. To further investigate these differences, an Individual Patient Data (IPD) meta-analysis of self-monitoring of blood pressure will be performed.

Methods and Analysis:

We will identify randomized trials that have compared patients with hypertension who are self-monitoring blood pressure with those who are not and invite trialists to provide IPD including clinic and/or ambulatory systolic and diastolic blood pressure at baseline and all follow-up points where both intervention and control groups were measured. Other data requested will include measurement methodology, length of follow up, co-interventions, baseline demographic (age, gender) and psychosocial factors (deprivation, quality of life), setting, intensity of self-monitoring, self-monitored blood pressure, co-morbidities, lifestyle factors (weight, smoking) and presence or not of antihypertensive treatment.

Data on all available patients will be included in order to take an intention-to-treat approach. A two-stage procedure for IPD meta-analysis, stratified by trial and taking into account age, sex, diabetes and baseline systolic BP will be used. Exploratory subgroup analyses will further investigate non-linear relationships between the pre-specified variables. Sensitivity analyses will assess the impact of trials which have and have not provided IPD.

Ethics and Dissemination:

This study does not include identifiable data. Results will be disseminated in a peer-reviewed publication and by international conference presentations.

Conclusion:

IPD analysis should help the understanding of which self-monitoring interventions for which patient groups are most effective in the control of blood pressure.

Key Words: Blood pressure, Hypertension, Self-management, Primary care

Article Summary

Article focus

- Self-monitoring of blood pressure is effective at reducing blood pressure in hypertension.
- This paper describes a protocol for an individual patient meta-analysis of previous clinical trials examining the effectiveness of self-monitoring of blood pressure in patients with hypertension

Key messages

- Previous study level meta-analyses have shown a considerable amount of heterogeneity between previous trials which cannot be fully accounted for by meta-regression.
- This study will use individual patient data to examine how differences in design, intervention components and patient sub-groups affect the impact of self-monitoring on blood pressure in hypertension.

Strengths and Limitations

- This study will gather all available individual patient data from previous trials examining the effectiveness of self-monitoring of blood pressure in hypertension totalling up to 10,000 randomised patients.
- It will be highly powered to compare the effectiveness of self-monitoring in different sub-groups which was not previously possible.
- This study is inherently retrospective but all proposed analyses will be agreed prior to conducting the investigation.

Background

Across Europe and the USA, around 30% of adults have or are being treated for hypertension, which is a key risk factor for cardiovascular disease, the largest cause of death worldwide.(1-4) Treatment of hypertension through lowering blood pressure results in significant reductions in both coronary artery disease and stroke.(5) Self-measurement of blood pressure (BP) has been shown in randomised control trials to reduce blood pressure over and above standard care.(6, 7) The improvements seen are thought to be due to an increased number of readings (providing a better estimation of underlying BP), removal of the white coat effect(8, 9) and increased patient involvement in their own treatment, resulting in more effective hypertension management.(10) Self-monitoring of blood pressure is an increasingly common part of hypertension management, is well tolerated by patients and has been shown to be a better predictor of end organ damage than office measurement.(11-16)

Previous systematic reviews and meta-analyses have found that self-monitoring reduces clinic blood pressure by an average of around 4 mmHg for systolic pressure and by around 1.5 mmHg for diastolic pressure, small, but significant reductions compared to conventional care.(17) (7) (18) However, these analyses found significant heterogeneity between the studies included (Systolic I^2 = 71.9%, Diastolic I^2 = 42.1%) that could not be accounted for by meta regression.(18) Similar reductions were seen in daytime ambulatory systolic blood pressure monitor (ABPM) but the small number of studies with such data included in the previous analysis made interpretation difficult.(18, 19)

Analysis by Bray *et al* suggested that when self-monitoring was accompanied by a co-intervention, participants were more likely to meet target BP but this did not explain remaining heterogeneity. Key issues in understanding this include differences in study populations such as age, gender, BMI, a previous cardiovascular event, and socioeconomic situation. Further differences in intervention, comparators and outcome measures may be important and there may be sub-groups of patients for whom self-monitoring is of greater or reduced benefit.

An individual patient data meta-analysis of these data may allow better discrimination of the causes of the underlying heterogeneity.

Methods

Aims and Objectives

This study will undertake an individual patient data meta-analysis of randomised trials of self-monitoring blood pressure using an intention to treat approach where possible. It will assess the evidence for the effectiveness of self-monitoring blood pressure, examine the effects of mediators of such effects and examine if particular sub-groups would particularly benefit from self-monitoring intervention. In addition we will aim to develop a prospective register of trials to facilitate on going analyses.

1) The primary objectives are to estimate the effect of self-monitoring blood pressure compared to standard care on:
   - systolic and diastolic clinic blood pressure at 12 month follow up
   - systolic and diastolic ambulatory blood pressure at 12 months follow up

- proportion controlled below the target specified in the individual trial at 12 months follow up

The effects at six and eighteen months will also be examined as the data allows as a secondary objective.

2) To use individual patient data to further explore the heterogeneity found previously and to assess the effect on outcome of the following where data allow: length of follow up, co-interventions, baseline demographic (age, gender) and psychosocial factors (deprivation, quality of life), setting, intensity of self-monitoring intervention, co-morbidities (eg history of diabetes, cardiovascular disease, stroke), lifestyle factors (diet, exercise, weight, smoking) and presence or not of antihypertensive treatment and the number of antihypertensive medications prescribed. This will allow better definition of which intervention to use with whom so as to better operationalise implementation of self-monitoring.

3) To develop a prospective register of trials to facilitate on going meta-analysis.

Criteria for considering studies for the IPD meta-analysis

All published and unpublished controlled trials where the authors are able to provide individual patient data will be included that fulfil the following criteria;

Population - patients with hypertension being managed on an outpatient basis.

Intervention – self-measurement of blood pressure without medical professional input plus or minus other co-interventions.

Comparator - no organised self-measurement of BP, although there may be some ad hoc measurement which would be difficult to prevent or assess.

Outcome - systolic and/or diastolic BP measured in clinic, or by ambulatory measurement.

Study design - randomised trial of at least 100 subjects followed up for at least 24 weeks.

Publication Date since 2000 (because changes in the technology used for self-monitoring make comparisons prior to this date less relevant).

Search strategy for identification of studies

Relevant electronic databases (Medline, Embase, Cochrane Library) will be searched for articles published from 2000. The search strategy has been designed to capture all the relevant literature concerning schedules for self-monitoring of blood pressure. The Medline search strategy is given in Appendix A and searches of reference lists of all retrieved papers will be performed. Articles for inclusion will be assessed independently by two reviewers. Non-randomised designs will be excluded. Data will be extracted independently by two team members with disagreements adjudicated by a third.

Trial eligibility and methodological quality assessment

All published and unpublished controlled trials will be included that assess self-measurement of blood pressure without medical professional input, if usual care did not include organised self-monitoring, and if a blood pressure outcome was available that had been taken independently of self-measurement (clinic or ambulatory measurement).

Data collection

Approaches will be made to all authors of trials that meet the inclusion criteria. The following data will be requested (if available);

Trial level data

- Setting (primary or secondary care)
- Population
  - inclusion and exclusion criteria
- Method of BP outcome measurement
  - monitor used
  - monitor validated?
  - arm used
  - number of readings used in analysis
  - other measurement criteria eg were repeated readings at least 1 min apart?
- Details about randomisation
  - allocation groups
  - method of generation of randomisation list
  - method of concealment of randomisation
  - stratification factors
- Intervention
  - details of training/education given (both for control and intervention)
  - targets used for intervention and control groups; if not specified for control concurrent national target will be used
  - type and frequency of self-monitoring.
  - any additional allocated intervention (ie co-intervention including tele-monitoring, self-management)
  - who titrates medication (health care professional /patient)
  - timing of trial follow up appointments
- Details about cost of intervention

Individual Patient data

- Demographic details
  - age and gender
- Past medical history (specific co-morbidities e.g. diabetes, cardiovascular disease)

- Medications prescribed at baseline and follow up
- Blood pressure readings (clinic, home and ambulatory where available)
    - baseline
    - follow up
- Allocation group
- Lifestyle factors
    - Smoking
    - Alcohol consumption
    - diet
    - weight
    - physical activity
- Psychosocial factors including
    - measures of deprivation e.g. Indices of Multiple Deprivation
    - measures of anxiety and depression
    - measures of quality of life e.g. EQ-5D^{TM}, SF36
- Patient satisfaction
- Costs
    - resource use
    - consultations
    - admissions
- Any new incidence of CV events or death
- Any clustering factors e.g. by practice

Data will be requested either in electronic or paper form and a desired format and coding will be specified. Trialists may supply data in the most convenient way open to them provided details of coding are supplied. The co-ordinating centre will ensure that data items are consistently derived, labelled and coded. Each trial group will be asked to nominate a trialist to lead in the collaboration.

Data validation strategy

Original data will be transferred and stored in a secure environment at the University of Oxford and copies will be made for use in the analyses. Trial details and summary measures will be cross-checked against published articles by two reviewers and inconsistencies will be discussed with the original trialist. Data from each trial will remain the property of each individual group.

Outcome measures

The primary outcomes will be the change in mean office systolic and diastolic blood pressure, change in ambulatory systolic and diastolic blood pressure and proportion of patients with office blood pressure below target between baseline and follow up. The primary outcome will be 12 months and outcomes will also be assessed at 6 and 18 months. Reporting of outcomes in the original trial report is not an eligibility requirement provided data are available.

Data analysis

A two-stage procedure for IPD meta-analysis (described below) will be adopted. Handling of missing data will be by complete case analysis, with sensitivity analyses using other methods including multiple imputation if possible.

The two stage analysis will use linear regression for continuous outcomes and logistic regression for proportions, aggregated across studies by random effects inverse variance methods. Intention-to-treat comparisons of outcomes between self-monitoring arm and comparator arm will be summarised as forest plots with I-squared statistics for heterogeneity. Analyses will be reported in subgroups, by level of self-monitoring intervention. This will be defined according to levels based on those previously described by Uhlig *et al.,*(20) as summarised in table 1. The level of intervention examined in each included study will be agreed by the co-ordinating centre and the relevant trialists prior to conducting the analysis. Regression models used in the primary analysis will be adjusted for patient characteristics (including age and sex), baseline blood pressure and medical history, where appropriate.

Further analyses will explore the effects of age (in 10 year age bands), sex, BMI (dichotomised around BMI of 30), baseline blood pressure (in 10 mmHg bands), number of medications prescribed at baseline and the presence of co-morbidities at baseline (myocardial infarction, stroke, diabetes, chronic kidney disease, obesity) on mean blood pressure change and blood pressure control at follow-up. Exploratory analyses will be conducted (where data are available) including the use and nature of co-interventions (e.g. aimed at medication adherence vs. behavioural change), planned intensity of self-monitoring (i.e. number of home readings), psychosocial factors (e.g. deprivation, quality of life), setting and type of healthcare professional involved (e.g. pharmacist vs. nurse vs. physician), lifestyle factors (e.g. diet, smoking, alcohol consumption, physical activity) and changes in antihypertensive treatment at follow-up.

In case of non-linear relationships between the pre-specified variables included in the model and outcome not detected by regression, and to further explore relationships where detected, these pre-specified variables will be further investigated in an exploratory analysis examining the individual categories (quintiles in the case of continuous variables).

The potential for bias due to non participation in the IPD will be investigated by comparing aggregate data from trials with and without IPD. Within trials complete case analysis will be used; sensitivity analyses will investigate other methods including, if appropriate, multiple imputation.

Discussion

It is hoped that individual patient data analysis will allow a greater understanding of observed between trial heterogeneity and lead to the identification of the characteristics of both the intervention and the individuals most likely to benefit from self-monitoring of blood pressure. This will enhance understanding of self-monitoring of blood pressure and enable better targeted and more effective use of this intervention.

Figures and tables

Table 1. Level of self-monitoring intervention

Level	Name	Description
Level 1	Self-monitoring with minimal additional contact	Self-monitoring without a text system or study phone calls. This could include one off leaflets with educational materials and initial instructions from a nurse on self-monitoring BP or a card for recording BP measurements.
Level 2	Self-monitoring with automated feedback or support	Web based or telephonic tools provide feedback or support. But no regular 1:1 contact.*
Level 3	Self-monitoring with an active intervention	Web based or telephonic tools provide feedback or support and education offered in regular classes including on hypertension self-management, and behaviour and lifestyle modifications. This could include self-management but not regular 1:1 contact.*
Level 4	Self-monitoring with significant tailored support	Individually tailored support from study personnel, pharmacist or a clinician throughout the intervention.* This could include checking BP / medication or education/ lifestyle counselling and may be in person, by telephone or via electronic means.

BP = Blood pressure

* 1:1 contact or support in this context refers to contact over and above that in usual care.

Appendix A:

Example Search Strategy (Medline)

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
Only trials published since 2000 eligible.

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1 blood pressure monitoring, ambulatory/
2 ((blood pressure or bp) adj3 (24h or 24hr? or 24-h or 24-hr? or 24 hour? or ambulatory or determin$ or measur$ or monitoring or monitor$ or self-measur$ or self-monitor$)).tw.
3 or/1-2
4 (home or self$).tw.
5 (telemedicine or tele-medicine or telemonitor$ or tele-monitor$).mp.
6 or/4-
7 randomized controlled trial.pt.
8 controlled clinical trial.pt.
9 randomized.ab.
10 placebo.ab.
11 drug therapy.fs.
12 randomly.ab.
13 trial.ab.
14 groups.ab.
15 or/7-14
16 animals/ not (humans/ and animals/)
17 15 not 16
18 3 and 6 and 17

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List of abbreviations

Blood pressure	-	BP
Body Mass Index	-	BMI
Cardiovascular Disease	-	CVD
Cardiovascular	-	CV
Diabetes mellitus	-	DM
Index of Multiple Deprivation	-	IMD
Individual Patient Data	-	IPD
Hypertension	-	HT

Authors' contributions:

The manuscript was prepared by KT and RM and edited by all authors, the methods and analysis plan was designed by RS, JS, SK, KT and RM, and reviewed by all authors. All Authors have read and reviewed the manuscript.

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Competing interests:

The author(s) declare that they have no competing interests apart from:

RJMcM has received research funding in terms of blood pressure monitors from Omron and Lloyds Healthcare. He has received expenses and an honorarium from the Japanese Society of Hypertension. FDRH has in the past received limited free or subsidised BP measuring devices from Microlife and Omron to support hypertension research, where there is no input from the companies to the design, funding, delivery, analysis or interpretation of that research. Stefano Omboni is a consultant of Biotechmed Ltd. (provider of blood pressure telemonitoring services). Sally Kerry has received research funding in terms of blood pressure monitors from Omron.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Criteria Met?
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Yes (Page 1)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	N/A
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes (Page 1)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes (Page 13)
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Yes (Page 13)
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes (Page 13)
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes (Page 4)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes (Page 4-5)
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Yes (Page 5-7)
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes (Pages 5 and 9)
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes (Page 9)

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes (Page 7)
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Yes (Page 5)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes (Page 7)
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes (Pages 6-7)
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes (Pages 4-5 and 7)
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes (Page 8)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes (Page 8)
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Yes (Page 8)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes (Page 8)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Yes (Page 8)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Individual patient data meta-analysis of self-monitoring of blood pressure (BP-SMART) Protocol paper

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Abstract

Introduction:

Self-monitoring of blood pressure is effective in reducing blood pressure in hypertension. However previous meta-analyses have shown a considerable amount of heterogeneity between studies, only part of which can be accounted for by meta-regression. This may be due to differences in design, recruited populations, intervention components, or results among patient sub-groups. To further investigate these differences, an Individual Patient Data (IPD) meta-analysis of self-monitoring of blood pressure will be performed.

Methods and Analysis:

We will identify randomized trials that have compared patients with hypertension who are self-monitoring blood pressure with those who are not and invite trialists to provide IPD including clinic and/or ambulatory systolic and diastolic blood pressure at baseline and all follow-up points where both intervention and control groups were measured. Other data requested will include measurement methodology, length of follow up, co-interventions, baseline demographic (age, gender) and psychosocial factors (deprivation, quality of life), setting, intensity of self-monitoring, self-monitored blood pressure, co-morbidities, lifestyle factors (weight, smoking) and presence or not of antihypertensive treatment.

Data on all available patients will be included in order to take an intention-to-treat approach. A two-stage procedure for IPD meta-analysis, stratified by trial and taking into account age, sex, diabetes and baseline systolic BP will be used. Exploratory subgroup analyses will further investigate non-linear relationships between the pre-specified variables. Sensitivity analyses will assess the impact of trials which have and have not provided IPD.

Ethics and Dissemination:

This study does not include identifiable data. Results will be disseminated in a peer-reviewed publication and by international conference presentations.

Conclusion:

IPD analysis should help the understanding of which self-monitoring interventions for which patient groups are most effective in the control of blood pressure.

Key Words: Blood pressure, Hypertension, Self-management, Primary care

Article Summary

Article focus

- Self-monitoring of blood pressure is effective at reducing blood pressure in hypertension.
- This paper describes a protocol for an individual patient meta-analysis of previous clinical trials examining the effectiveness of self-monitoring of blood pressure in patients with hypertension

Key messages

- Previous study level meta-analyses have shown a considerable amount of heterogeneity between previous trials which cannot be fully accounted for by meta-regression.
- This study will use individual patient data to examine how differences in design, intervention components and patient sub-groups affect the impact of self-monitoring on blood pressure in hypertension.

Strengths and Limitations

- This study will gather all available individual patient data from previous trials examining the effectiveness of self-monitoring of blood pressure in hypertension totalling up to 10,000 randomised patients.
- It will be highly powered to compare the effectiveness of self-monitoring in different sub-groups which was not previously possible.
- This study is inherently retrospective but all proposed analyses will be agreed prior to conducting the investigation.

Background

Across Europe and the USA, around 30% of adults have or are being treated for hypertension, which is a key risk factor for cardiovascular disease, the largest cause of death worldwide.(1-4) Treatment of hypertension through lowering blood pressure results in significant reductions in both coronary artery disease and stroke.(5) Self-measurement of blood pressure (BP) has been shown in randomised control trials to reduce blood pressure over and above standard care.(6, 7) The improvements seen are thought to be due to increased patient involvement in their own treatment, resulting in more effective hypertension management.(8) Self-monitoring of blood pressure is an increasingly common part of hypertension management, is well tolerated by patients and has been shown to be a better predictor of end organ damage than office measurement.(9-14)

Previous systematic reviews and meta-analyses have found that self-monitoring reduces clinic blood pressure by an average of around 4 mmHg for systolic pressure and by around 1.5 mmHg for diastolic pressure, small, but significant reductions compared to conventional care.(15) (7) (16) However, these analyses found significant heterogeneity between the studies included (Systolic I^2 = 71.9%, Diastolic I^2 = 42.1%) that could not be accounted for by meta regression.(16) Similar reductions were seen in daytime ambulatory systolic blood pressure monitor (ABPM) but the small number of studies with such data included in the previous analysis made interpretation difficult.(16, 17)

Analysis by Bray *et al* suggested that when self-monitoring was accompanied by a co-intervention, participants were more likely to meet target BP but this did not explain remaining heterogeneity. Key issues in understanding this include differences in study populations such as age, gender, BMI, a previous cardiovascular event, and socioeconomic situation. Subgroup analyses from a previous summary meta-analysis suggests that the observed heterogeneity can be explained in part, due to co-interventions such as telemonitoring and use of self-titration and the setting in which the intervention is delivered.(18) Further differences in intervention, comparators and outcome measures may be important and there may be sub-groups of patients for whom self-monitoring is of greater or reduced benefit.

An individual patient data meta-analysis of these data may allow better discrimination of the causes of the underlying heterogeneity.

Methods

Aims and Objectives

This study will undertake an individual patient data meta-analysis of randomised trials of self-monitoring blood pressure using an intention to treat approach where possible. It will assess the evidence for the effectiveness of self-monitoring blood pressure, examine the effects of mediators of such effects and examine if particular sub-groups would particularly benefit from self-monitoring intervention. In addition we will aim to develop a prospective register of trials to facilitate on going analyses.

1) The primary objectives are to estimate the effect of self-monitoring blood pressure compared to standard care on:

- systolic and diastolic clinic blood pressure at 12 month follow up
- systolic and diastolic ambulatory blood pressure at 12 months follow up
- proportion controlled below the target specified in the individual trial at 12 months follow up

The effects at six and eighteen months will also be examined as the data allows as a secondary objective.

2) To use individual patient data to further explore the heterogeneity found previously and to assess the effect on outcome of the following where data allow: length of follow up, co-interventions, baseline demographic (age, gender) and psychosocial factors (deprivation, quality of life), setting, intensity of self-monitoring intervention, co-morbidities (eg history of diabetes, cardiovascular disease, stroke), lifestyle factors (diet, exercise, weight, smoking) and presence or not of antihypertensive treatment and the number of antihypertensive medications prescribed. This will allow better definition of which intervention to use with whom so as to better operationalise implementation of self-monitoring.

3) To develop a prospective register of trials to facilitate on going meta-analysis.

Criteria for considering studies for the IPD meta-analysis

All published and unpublished controlled trials where the authors are able to provide individual patient data will be included that fulfil the following criteria;

Population - patients with hypertension being managed on an outpatient basis.

Intervention – self-measurement of blood pressure without medical professional input plus or minus other co-interventions.

Comparator - no organised self-measurement of BP, although there may be some ad hoc measurement which would be difficult to prevent or assess.

Outcome - systolic and/or diastolic BP measured in clinic, or by daytime ambulatory measurement.

Study design - randomised trial of at least 100 subjects followed up for at least 24 weeks.

Publication Date since 2000 (because changes in the technology used for self-monitoring make comparisons prior to this date less relevant).

Search strategy for identification of studies

Relevant electronic databases (Medline, Embase, Cochrane Library) will be searched for articles published from 2000. The search strategy has been designed to capture all the relevant literature concerning schedules for self-monitoring of blood pressure. The Medline search strategy is given in Appendix A and searches of reference lists of all retrieved papers will be performed. Articles for inclusion will be assessed independently by two reviewers. Non-randomised designs will be excluded. Data will be extracted independently by two team members with disagreements adjudicated by a third. We will study the reference lists of

included articles and ask contributing authors if they have, or are aware of any unpublished data which might be included in the review.

Trial eligibility and methodological quality assessment

All published and unpublished controlled trials will be included that assess self-measurement of blood pressure without medical professional input, if usual care did not include organised self-monitoring, and if a blood pressure outcome was available that had been taken independently of self-measurement (clinic or ambulatory measurement).

Assessment of the quality of included trials is controversial.(19) Self-monitoring studies are generally un-blinded for obvious reasons. We will assess the quality of studies in terms of the presence of randomisation, the methodology of outcome assessment, intention-to-treat analyses and attrition rates.(20) We will initially include all studies, and then perform sensitivity analyses considering the potential effect of excluding studies which may be confounded for these reasons.

Data collection

Approaches will be made to all authors of trials that meet the inclusion criteria. The following data will be requested (if available);

Trial level data

- Setting (primary or secondary care)
- Population
  - inclusion and exclusion criteria
- Method of BP outcome measurement
  - monitor used
  - monitor validated?
  - arm used
  - number of readings used in analysis
  - other measurement criteria eg were repeated readings at least 1 min apart?
- Details about randomisation
  - allocation groups
  - method of generation of randomisation list
  - method of concealment of randomisation
  - stratification factors
- Intervention
  - details of training/education given (both for control and intervention)
  - targets used for intervention and control groups; if not specified for control concurrent national target will be used
  - type and frequency of self-monitoring.

- any additional allocated intervention (ie co-intervention including tele-monitoring, self-management)
- who titrates medication (health care professional /patient)
- timing of trial follow up appointments

- Details about cost of intervention

Individual Patient data

- Demographic details
  - age and gender
- Past medical history (specific co-morbidities e.g. diabetes, cardiovascular disease)
- Number of medications prescribed at baseline and follow up
- Blood pressure readings (clinic, home and ambulatory where available)
  - baseline
  - follow up
- Allocation group
- Lifestyle factors
  - Smoking
  - Alcohol consumption
  - diet
  - weight
  - physical activity
- Psychosocial factors including
  - measures of deprivation e.g. Indices of Multiple Deprivation
  - measures of anxiety and depression
  - measures of quality of life e.g. EQ-5D^{TM}, SF36
- Patient satisfaction
- Costs
  - resource use
  - consultations
  - admissions
- Any new incidence of CV events or death
- Any clustering factors e.g. by practice

Data will be requested either in electronic or paper form and a desired format and coding will be specified. Trialists may supply data in the most convenient way open to them provided details of coding are supplied. The co-ordinating centre will ensure that data items are consistently derived, labelled and coded. Each trial group will be asked to nominate a trialist to lead in the collaboration.

Data validation strategy

Original data will be transferred and stored in a secure environment at the University of Oxford and copies will be made for use in the analyses. Trial details and summary measures will be cross-checked against published articles by two reviewers and inconsistencies will be

discussed with the original trialist. Data from each trial will remain the property of each individual group.

Outcome measures

The primary outcomes will be the change in mean office systolic and diastolic blood pressure, change in ambulatory systolic and diastolic blood pressure and proportion of patients with office blood pressure below target between baseline and follow up. The primary outcome will be 12 months and outcomes will also be assessed at 6 and 18 months. Reporting of outcomes in the original trial report is not an eligibility requirement provided data are available.

Data analysis

Data will be initially tabulated to include important attributes of each trial and to assess comparability, for example of treatment targets.

A two-stage procedure for IPD meta-analysis (described below) will be adopted. Handling of missing data will be by complete case analysis, with sensitivity analyses using other methods including multiple imputation if possible.

The two stage analysis will use linear regression for continuous outcomes and logistic regression for proportions, aggregated across studies by random effects inverse variance methods. Intention-to-treat comparisons of outcomes between self-monitoring arm and comparator arm will be summarised as forest plots with I-squared statistics for heterogeneity. Analyses will be reported in subgroups, by level of self-monitoring intervention. This will be defined according to levels based on those previously described by Uhlig *et al.,*(21) as summarised in table 1. The level of intervention examined in each included study will be agreed by the co-ordinating centre and the relevant trialists prior to conducting the analysis. Regression models used in the primary analysis will be adjusted for patient characteristics (including age and sex), baseline blood pressure and medical history, where appropriate.

Further analyses will explore the effects of age (in 10 year age bands), sex, BMI (dichotomised around BMI of 30), baseline blood pressure (in 10 mmHg bands), number of medications prescribed at baseline and the presence of co-morbidities at baseline (myocardial infarction, stroke, diabetes, chronic kidney disease, obesity) on mean blood pressure change and blood pressure control at follow-up. Exploratory analyses will be conducted (where data are available) including the use and nature of co-interventions (e.g. aimed at medication adherence vs. behavioural change), planned intensity of self-monitoring (i.e. number of home readings), psychosocial factors (e.g. deprivation, quality of life), setting and type of healthcare professional involved (e.g. pharmacist vs. nurse vs. physician), lifestyle factors (e.g. diet, smoking, alcohol consumption, physical activity) and changes in antihypertensive treatment at follow-up and the impact on mean arterial blood pressure (MAP).

In case of non-linear relationships between the pre-specified variables included in the model and outcome not detected by regression, and to further explore relationships where

detected, these pre-specified variables will be further investigated in an exploratory analysis examining the individual categories (quintiles in the case of continuous variables).

The potential for bias due to non-participation in the IPD will be investigated by comparing aggregate data from eligible trials with and without IPD. Notwithstanding this and the impact of the inclusion criteria (which exclude studies with small populations and /or short follow-up), publication bias for the primary outcome will be explored using Eggar's methods.(22) For included trials a complete case analysis approach will be used; sensitivity analyses will investigate other methods including, if appropriate, multiple imputation.

Discussion

It is hoped that individual patient data analysis will allow a greater understanding of observed between trial heterogeneity and lead to the identification of the characteristics of both the intervention and the individuals most likely to benefit from self-monitoring of blood pressure. This will enhance understanding of self-monitoring of blood pressure and enable better targeted and more effective use of this intervention.

Figures and tables

Table 1. Level of self-monitoring intervention

Level	Name	Description
Level 1	Self-monitoring with minimal additional contact	Self-monitoring without a text system or study phone calls. This could include one off leaflets with educational materials and initial instructions from a nurse on self-monitoring BP or a card for recording BP measurements.
Level 2	Self-monitoring with automated feedback or support	Web based or telephonic tools provide feedback or support. But no regular 1:1 contact.*
Level 3	Self-monitoring with an active intervention	Web based or telephonic tools provide feedback or support and education offered in regular classes including on hypertension self-management, and behaviour and lifestyle modifications. This could include self-management but not regular 1:1 contact.*
Level 4	Self-monitoring with significant tailored support	Individually tailored support from study personnel, pharmacist or a clinician throughout the intervention.* This could include checking BP / medication or education/ lifestyle counselling and may be in person, by telephone or via electronic means.

BP = Blood pressure

* 1:1 contact or support in this context refers to contact over and above that in usual care.

Appendix A:

Example Search Strategy (Medline)

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
Only trials published since 2000 eligible.

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1 blood pressure monitoring, ambulatory/
2 ((blood pressure or bp) adj3 (24h or 24hr? or 24-h or 24-hr? or 24 hour? or ambulatory or determin$ or measur$ or monitoring or monitor$ or self-measur$ or self-monitor$)).tw.
3 or/1-2
4 (home or self$).tw.
5 (telemedicine or tele-medicine or telemonitor$ or tele-monitor$).mp.
6 or/4-
7 randomized controlled trial.pt.
8 controlled clinical trial.pt.
9 randomized.ab.
10 placebo.ab.
11 drug therapy.fs.
12 randomly.ab.
13 trial.ab.
14 groups.ab.
15 or/7-14
16 animals/ not (humans/ and animals/)
17 15 not 16
18 3 and 6 and 17

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List of abbreviations

Blood pressure	-	BP
Body Mass Index	-	BMI
Cardiovascular Disease	-	CVD
Cardiovascular	-	CV
Diabetes mellitus	-	DM
Index of Multiple Deprivation	-	IMD
Individual Patient Data	-	IPD
Hypertension	-	HT

Authors' contributions:

The manuscript was prepared by KT and RM and edited by all authors, the methods and analysis plan was designed by RS, JS, SK, KT and RM, and reviewed by all authors. All Authors have read and reviewed the manuscript.

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Competing interests:

The author(s) declare that they have no competing interests apart from:

RJMcM has received research funding in terms of blood pressure monitors from Omron and Lloyds Healthcare. He has received expenses and an honorarium from the Japanese Society of Hypertension. FDRH has in the past received limited free or subsidised BP measuring devices from Microlife and Omron to support hypertension research, where there is no input from the companies to the design, funding, delivery, analysis or interpretation of that research. Stefano Omboni is a consultant of Biotechmed Ltd. (provider of blood pressure telemonitoring services). Sally Kerry has received research funding in terms of blood pressure monitors from Omron.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Criteria Met?
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Yes (Page 1)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	N/A
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes (Page 1)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes (Page 13)
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Yes (Page 13)
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes (Page 13)
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes (Page 4)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes (Page 4-5)
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Yes (Page 5-7)
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes (Pages 5 and 9)
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Yes (Page 9)

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes (Page 7)
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Yes (Page 5)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes (Page 7)
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes (Pages 6-7)
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes (Pages 4-5 and 7)
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes (Page 8)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes (Page 8)
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Yes (Page 8)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes (Page 8)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Yes (Page 8)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Appendix A:

Example Search Strategy (Medline)

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
Only trials published since 2000 eligible.

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1 blood pressure monitoring, ambulatory/
2 ((blood pressure or bp) adj3 (24h or 24hr? or 24-h or 24-hr? or 24 hour? or ambulatory or determin$ or measur$ or monitoring or monitor$ or self-measur$ or self-monitor$)).tw.
3 or/1-2
4 (home or self$).tw.
5 (telemedicine or tele-medicine or telemonitor$ or tele-monitor$).mp.
6 or/4-
7 randomized controlled trial.pt.
8 controlled clinical trial.pt.
9 randomized.ab.
10 placebo.ab.
11 drug therapy.fs.
12 randomly.ab.
13 trial.ab.
14 groups.ab.
15 or/7-14
16 animals/ not (humans/ and animals/)
17 15 not 16
18 3 and 6 and 17

Correction

Tucker KL, Sheppard JP, Stevens R, *et al*. Individual patient data meta-analysis of self-monitoring of blood pressure (BP-SMART): a protocol. *BMJ Open* 2015;5:e008532.

The affiliation for Professor Gianfranco Parati, a co-author on this paper, is incorrect and should be: Department of Cardiovascular, Neural and Metabolic Sciences, San Luca Hospital, Istituto Auxologico Italiano, Milan, Italy & Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy.

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