TASMIN-SR Statistical Analysis Plan

Baseline characteristics will be summarised by treatment arm, to include patients’ demographic details and past medical history.

Primary analysis
The primary outcome will be the mean of the 2nd and 3rd reading of blood pressure obtained from a series of 6 BP readings taken at one-minute intervals by an electronic sphygmanometer. Mixed model analysis will be used to examine differences between intervention and control patients within subject reductions of systolic blood pressure between baseline and 12 months. The primary analysis will include all subjects with complete data at follow-up. The analysis will be adjusted by general practice (as a random effect), baseline blood pressure (fixed effect), gender (fixed effect) and high risk group (fixed effect).

Secondary analysis
The effect of intervention on systolic BP at 6 and diastolic BP at 6 and 12 months will be explored with mixed model analysis. All other measurements viz. percentage change in target BP range, change in: pulse rate, self-management self-efficacy, lifestyle behaviours, health-related quality of life, anxiety, attitudes to health and healthcare, use of other self-management strategies will also be analysed using mixed modelling. The number of adverse events will be compared using generalised linear model. Change in BP measurement method preference (an ordinal variable) will be analysed using ordinal logistic regression. The reasons for non-participation will be compared using a chi-square test

Planned subgroup analyses will be of older versus younger (threshold 65 years), males vs. females, better controlled at baseline vs. worse control at baseline (threshold 145 systolic), the different risk groups and deprivation.

A sensitivity analysis of the primary outcome will be performed to examine the potential effect of missing data. This will include multiple imputation, last value carried forward, mean of the series.

All analyses will be performed at the end of the trial when all the data have been collected.

No interim analyses will be performed.

Original draft Andrea Roalfe 14/2/2011
Revised Sayeed Haque 28/06/2011

Revision of Analysis Plan
The primary analysis will include all available participants, i.e. all of those with complete data from follow-up, and will be performed at the end of the trial after all
data has been collected. A mixed model analysis will be used to examine differences between intervention and control systolic BP at twelve months, adjusting for practice (as a random effect), baseline BP, gender, and high risk group. Planned sub group analyses will be of older vs younger (65 as threshold), males vs females, better controlled at baseline vs worse controlled at baseline (threshold 145 systolic), the different risk groups and deprivation. Sensitivity analyses will examine the potential effect of missing data. These will include multiple imputation, replacement of missing data by the most recent previous data or by the mean of the series. Any deviation from the original statistical plan will be described in the final report and publications.

The Analysis Plan was further revised as above during the protocol paper submission process prior to analysis (Sayeed Haque and Richard McManus 20/3/2013):

The last patient was followed up on 03/01/2013 and the database was finally locked on 17/07/2013 at which point the primary analysis was undertaken.
PROTOCOL

Targets and self management for the control of blood pressure in stroke and at risk groups (TASMIN-SR): A randomised controlled trial

Protocol identifying number:
Date: V1 20/8/10; revised V1.1 06/01/2012

Acronym

TASMIN-SR

Name and address of the sponsor

University of Birmingham
Edgbaston
Birmingham B15 2TT

Chief Investigator

Prof Richard McManus
Primary Care Clinical Sciences
University of Birmingham
Edgbaston
Birmingham B15 2TT

The need for a trial

What is the problem to be addressed?
The recently concluded TASMINH2 trial \(^1,2\) found that self management of hypertension (self measurement of blood pressure and self titration of medication) resulted in significantly lower (5.4mmHg) systolic blood pressure after one year as compared to usual care. However, the study included few people in high risk groups such as diabetes or Chronic Kidney Disease (CKD), in whom the effect size appeared to be smaller, principally because blood pressure lowering in the control group seemed to be greater than in controls without diabetes or CKD. A trial assessing the added value of self management in high risk groups over and above usual care is therefore required. Furthermore, in TASMINH2 telemetry was used to allow patients to transmit results to the research group as a safety feature. Action based on this where patients had not acted on persistently raised or low blood pressure, consisting of a phone call from the research group was only required in 3% of the self monitoring patients. Telemetry is not currently widely available in the UK and the standards for transfer of electronic blood pressure readings are not sufficiently widely adopted to allow such readings to be easily integrated into clinical record systems. A self management system that avoided telemetry might be more cost effective and easier to integrate into daily practice.

Additionally, lessons learnt from both the TASMINH2 qualitative work and current pilot work will be used to improve the intervention for future implementation. The
first is that only 10% of individuals in TASMIN2 required more than three medication changes, and some of these patients found it difficult to obtain the extra titration plan they required. Therefore the intervention will be updated to include an initial three-step titration plan rather than the original two-step plan, to reduce the number of subsequent appointments required for a further titration plan to be devised. Secondly GPs in TASMINH2 were not directly involved in the intervention, aside from devising the titration plans. This became apparent in the professional interviews where several of them had difficulty remembering what they had done. To increase the ability to translate this research into practice, GPs will receive each patient’s monthly blood pressure readings directly, hopefully better integrating them in the process of the self-management and maintaining their engagement in the study. Thirdly, as high and low readings were colour-coded as RED, this caused some confusion in patients regarding what action to take. Therefore it is proposed to change low readings to be classified as Blue readings on the algorithm. Finally, some patients found it difficult to remember what actions they should take and so the blood pressure recording paperwork will be updated ensuring that the monthly required action is recorded in the same place as the blood pressure measurements. Additionally, the form will have less open-ended free text questions, and be more structured to help remind patients of the appropriate action to take.

Therefore, the problem to be addressed is to determine whether the benefits from blood pressure lowering observed with self management and telemonitoring in a general population of people with uncontrolled hypertension can, in an improved form, translate to a population of people at high cardiovascular risk by virtue of co-existing disease (i.e., stroke/TIA, IHD, diabetes, CKD), without using telemetry.

**Research Questions**

The main research questions are:

1. Does self-management of blood pressure (self monitoring plus self titration of anti-hypertensive medication) result in better control of BP in people with stroke and other at-risk conditions compared to usual care?

2. Is self management of blood pressure in people with stroke and other at-risk conditions achievable in routine practice and is it acceptable to patients?

3. What is the relationship between self management of blood pressure, self-efficacy, lifestyle behaviours, patient attitudes to health and health care and use of other self care strategies in people with stroke and other at-risk conditions?
4. Is self management of blood pressure in people with stroke and other at-risk conditions cost effective?

**Why is a trial needed now?**

The potential benefit from optimal blood pressure lowering in patients at high cardiovascular risk following stroke or TIA, coronary heart disease or with diabetes or CKD is large. The HOPE trial showed that treatment with an ACE inhibitor was beneficial for people at high risk of cardiovascular disease over and above standard care and including those with normal blood pressure. In this trial, 9297 high-risk patients (55 years of age or older) who had evidence of vascular disease or diabetes plus one other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure were randomly assigned to receive ramipril (10 mg once per day orally) or placebo and followed up for 5 years. The primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes. The effects of ramipril were positive: the primary outcome occurred in 651 (14%) of ramipril patients compared to 826 (18%) of the placebo group (relative risk, 0.78; 95% confidence interval, 0.70 to 0.86; p <0.001). Treatment with ramipril also reduced the rates of death from cardiovascular causes (6.1%, vs. 8.1% in the placebo group; relative risk, 0.74; p <0.001), myocardial infarction (9.9% vs. 12.3%; relative risk, 0.80; p <0.001), stroke (3.4% vs. 4.9%; relative risk, 0.68; p<0.001), death from any cause (10.4% vs. 12.2%; relative risk, 0.84; p=0.005), revascularization procedures (16.0% vs. 18.3%; relative risk, 0.85; p=0.002), cardiac arrest (0.8% vs. 1.3%; relative risk, 0.63; p=0.03), heart failure (9.0% vs. 11.5%; relative risk, 0.77; p<0.001), and complications related to diabetes (6.4% vs. 7.6%; relative risk, 0.84; p=0.03).

Considering individual high risk groups, the PROGRESS trial demonstrated that blood pressure lowering is beneficial in reducing risk of stroke amongst both hypertensive and non-hypertensive individuals with a history of stroke or TIA. For people with coronary heart disease, blood pressure lowering has the same risk reduction as in those without coronary heart disease (relative risk 0.85 (0.79, 0.91) vs. 0.84 (0.79, 0.90) respectively) however the higher absolute risk in CHD means that for a given blood pressure reduction the absolute benefits are greater. The Hypertension Optimal Treatment trial showed no difference in outcome for diastolic blood pressure targets below 90mmHg, apart from in people with diabetes for whom the 80mmHg group did better. The blood pressure trialists have shown similar relative risk reductions from blood pressure lowering in diabetes compared to other groups, again with higher absolute risk reductions. In subgroup analysis of the HOPE study, people with chronic kidney disease received equivalent benefit from ramipril as those without kidney disease.

Guidelines for the various at risk groups vary in terms of recommendations for blood pressure lowering. The National Clinical Guideline for stroke recommends that unless there is bilateral carotid artery stenosis, the target blood pressure for secondary prevention of stroke and TIA should be 130/80mmHg. The British Hypertension Society guidelines suggest the same target. NICE guidelines for diabetes, suggest a lower blood pressure target than recommended for essential hypertension namely
140/80mmHg or 130/75mmHg in cases of proteinuria. For coronary heart disease, standard blood pressure targets are recommended i.e., 140/90 mmHg or below, and for chronic kidney disease NICE also recommend a target of 140/90 mmHg unless there is accompanying diabetes or proteinuria (ACR > 70 mg/mmol) in which case the target drops to 130/80 mmHg. The BHS guidelines however, suggest a target of <130/80 mmHg for stroke/ TIA, diabetes, CKD3 (without proteinuria), CHD and MI allowing uniformity across the range of high risk groups.10

Data from national and international surveys suggest that blood pressure control is sub-optimal.11 Novel interventions are therefore needed to improve this and as most blood pressure management is undertaken in primary care, where hypertension is the commonest long term condition seen by GPs, it is appropriate that interventions are delivered in this setting.

The TASMINH2 trial showed that self management of hypertension in people with poorly controlled hypertension is effective, leading to a 5.4 mmHg reduction in systolic blood pressure after one year compared to usual care.12 Therefore self management appears an attractive option to reduce blood pressure in other circumstances, and might be particularly relevant where cardiovascular risk is greatest, for example following a cerebrovascular event. Self-management can encompass a wide range of behaviours in addition to medication titration and monitoring of symptoms, such as an individual’s ability to manage physical, psychosocial and lifestyle behaviours related to chronic illness. Self-efficacy, which is a person’s confidence to be able to carry out behaviours to achieve a desired goal, has been found to be the strongest predictor of a person’s ability to change risky health behaviours by taking action, and an important characteristic for successful self-management.13 It is unclear what the relationship is between self-monitoring of BP, self-efficacy and health behaviour modification; it is possible that the self-monitoring aspect provides feedback to the individual about their BP of which they would otherwise be unaware. This in turn may promote self-management of health behaviours in those with higher levels of self-efficacy. The TASMINH-SR trial sets out to investigate whether self-management is effective and cost effective in people with stroke and other high risk conditions.

**Has a systematic review been carried out and what were the findings?**

Many studies have explored self monitoring of blood pressure in hypertensive populations, with a recent systematic review examining the effects of self monitoring, both with and without co-interventions using data from 25 randomised trials.14 This found that self monitoring results in small reductions in blood pressure of the order of -3.82mmHg (95 % CI -5.61, -2.03) and -1.45 mmHg (-1.95, -0.94) for systolic and diastolic respectively. However, there was significant heterogeneity between studies which meta-regression showed could be partially accounted for by the use of additional co-interventions: studies where such co-interventions were present appeared to result in greater reductions in blood pressure.

No systematic review has been carried out regarding self management of blood pressure specifically in a high cardiovascular risk population. Only two randomised
studies $^{15,16}$ have evaluated the effects of self titration of blood pressure and both were
in hypertensive populations with poor blood pressure control. The latter was a small
case Canadian study with a 8-week follow up, and the former a large UK RCT with
follow up of one year, and both found that self-management achieved a significant
reduction in blood pressure compared to usual care. In the case of the TASMINH2
trial, systolic blood pressure was reduced by 5.4mmHg in the intervention group
compared to the control group.

The proposed trial will extend the current knowledge by:

1. Developing the self management intervention taking into account experience
gained in the TASMINH2 trial
2. Assessing whether the intervention can be effective without a telemonitoring
aspect.
3. Providing evidence as to whether self management can effectively and
feasibly lead to better control of blood pressure in patients with stroke and
other at-risk conditions.

**How will the results of this trial be used?**

The results of the trial will be directly applicable to primary care in the UK. Should
self management of blood pressure in people with stroke and other high risk
conditions be a successful strategy then it would be applicable to many hundreds of
thousands of individuals in the UK and beyond.

**Potential Benefits**

If self management of blood pressure in people with stroke and other high risk
conditions led to lower blood pressure through more appropriate intensive treatment
then this would lead to reductions in morbidity and mortality, particularly in terms of
recurrent stroke and coronary heart disease. As these conditions are high risk, the
absolute benefit in terms of risk would be higher than for essential hypertension alone.
Evidence from other fields has also shown that higher self-efficacy leads to improved
self-management outcomes and can modify health behaviours over and above
treatment intensification (e.g., Holloway & Watson, $^{17}$; Kobau & Dilorio $^{18}$).

**The Trial**

Trial design
TASMIN-SR will be a primary-care based, unblinded, randomised controlled trial, of
self management of blood pressure consisting of self monitoring with self titration of
anti-hypertensive medication in people with stroke and other high risk conditions.
Recruitment will be achieved through the Midlands Research Practices Consortium
(MidReC) and the Primary Care Research Network. Patients will be invited to participate if they have a diagnosis of stroke/TIA, diabetes, CKD3, CABG, MI or angina, and their blood pressure is above 130/80mmHg. Patients will be randomised using an internet based system with telephone back up. In order to minimise the effect of having an unblinded design, researchers measuring blood pressure for the primary outcome will use validated automated electronic sphygmomanometers where measurement will not be affected by knowledge of allocation. We will stratify by practice and minimisation will be used to take into account, gender, age, high risk group (CVD, diabetes, CKD3, CHD) and baseline BP. The primary outcome of the trial will be difference in the reduction of office SBP from baseline to 12 month follow up between intervention and control

Sample

Eligibility criteria will be age above 35, have had a diagnosis of stroke/TIA, diabetes, CKD3, MI, angina, or CABG, and systolic blood pressure greater than 130/80 mmHg. Exclusion criteria will include inability to self-monitor such as dementia or score over 10 on the short orientation memory concentration test (and with no carer support), postural hypotension (fall in SBP > 20 mmHg after 1 minute standing), taking more than three anti-hypertensive medications, taking part in a current blood pressure study or previously taken part in TASMINH2, terminal disease, pregnant, BP not managed by the GP and acute cardiovascular event in the last 3 months.

Recruitment

A sample size of 243 people per group is required for 90% power assuming a standard deviation of 17 mm Hg (which lies between that obtained in TASMINH and TASMINH2) and a difference of at least 5 mm Hg between intervention and control groups which represents a clinically significant decrease in BP and is in line with the reduction observed in TASMINH2. A difference of 5 mm Hg would result in around 20% reduction in stroke risk and 10% coronary heart disease risk. Based on the follow up rates in the TASMINH 19 and TASMINH2 20 studies, a 10% drop out rate during follow up is assumed meaning that a sample of 270 per group will need to be randomised; a total of 540 patients altogether.

We aim to recruit patients and practices to the trial over a period of eight months. Based on TASMINH2 and our work in stroke populations, we expect 30% of invited patients to attend a baseline research clinic, and 50% of these to be eligible for the study. Based on practice-based pilot computer searches we have estimated that in a practice with an average size of 6000 patients, 2.5% will be eligible for invitation. This means we will need 25 practices to recruit the required number of participants (average of 22 patients per practice being randomised). We aim to recruit these practices via 5 national primary care research networks, with each network recruiting between 100-105 patients from 5 practices. For each site the relevant primary care physicians will retain medical responsibility for the trial patients.
Potentially eligible patients will be identified by trained practice nurses searching electronic practice-based registers for people having a Read code of stroke or TIA, Diabetes, CKD3, Angina, CABG, or MI, and whose last systolic blood pressure was recorded to be greater than 145 mmHg (the higher BP is because in TASMINH2 we found that many people were not eligible when invited on the randomisation BP criteria as BP was lower when measured by the research team. Having a higher BP level at invitation will ensure efficient recruitment). The identified patients, and their carers where appropriate, will be invited to attend an initial clinic by postal invitation including a covering letter from the practice and a participant information sheet from the study team. Included with the letter of invitation to take part in the trial will be a form for people to voluntarily return should they wish to decline the invitation which will ask them for their reasons for decline, and permission to access their medical records as well as requesting basic demographic details.

**Flow through the study**

At baseline all patients will attend a research clinic at which the study will be explained and informed consent gained. Following this, measurement of blood pressure will occur using a validated automated electronic sphygmomanometer. Six seated blood pressure readings will be taken at 1-minute intervals, of which the mean of the 2nd and 3rd reading will comprise the primary outcome. Blood pressure will also be measured after 1-minute in a standing position to enable assessment of postural hypotension. Once the other exclusion criteria have been assessed (memory score >10 and no carer willing to assist, taking more than three anti-hypertensive medications, blood pressure not managed by the GP, not taking part in another BP study or previously took part in TASMINH2), height and weight measurements will be performed, and patients will be asked to complete a questionnaire regarding demographics, past medical history, BP measurement method preference, use of self-management strategies, and attitudes to health and healthcare (rejection of medical authority, consumerism and individual responsibility for health). Finally, they will be given information and advice from the researcher on health behaviours that can lead to improved BP such as following a healthy diet, increasing exercise, decreasing alcohol intake and salt consumption, and quitting smoking.

Patients will be randomised using an internet based system with telephone back up to either usual care or self management. All patients will be given a diary to assess daily lifestyle behaviours (adapted version of the SLIQ and The Dietary Quality Score) and self-management self-efficacy (adapted diabetes mellitus 2 self-efficacy scale) which they will be asked to complete everyday for one week starting the first Monday of the month after their baseline appointment. Once completed, they will be asked to return these to the research team using a provided freepost envelope. Patients randomised to usual care will be asked to book an appointment for a routine blood pressure check and medication review with their usual GP. Patients randomised to self management will be asked to make an appointment with the research team for a group training session on how to monitor their blood pressure, returning a week later for an
individual appointment which will cover the self titration aspect of the intervention. If necessary a third training session will be offered for additional support. Following successful completion of the training, participants will be asked to make an appointment with their physician for a routine blood pressure check and to establish the titration plan to allow them to make any necessary medication changes based on their home readings. Intervention patients will return to the GP should they require additional steps devising on their titration plan. Additionally, in the case of very high or very low blood pressure patients will be asked to attend the GP or nurse for a check. Figure 1 shows flow through the study. See below for follow up details. Should participants not be able to complete all aspects of the training successfully, where appropriate they will be given the option to just self-monitor blood pressure without self-titration of medications.
**Trial Interventions**

Usual care will consist of the participant seeing their GP and/or nurse for routine blood pressure measurement and/or adjustment of medication at the discretion of the health professional.

Self management will consist of self monitoring of blood pressure with self titration of medication following a predetermined 3-step plan, dependent on the self monitored BP readings. A two step plan has been tested previously in the TASMINH2 trial and patients and their physicians were able to follow it, however 18% of patients
randomised to the intervention group had to return for a third, fourth or fifth step. By switching to a three step titration plan then it is anticipated that the consultation rate will be lower as only 10% of individuals in the previous trial required more than three steps.

**Blood Pressure Self Monitoring:** Blood pressure targets for different morbidities vary depending on the guidelines used. The British Hypertension Society guidelines and Joint British Societies Guidelines suggest that the BP target for patients with stroke/TIA, diabetes (in the absence of proteinuria), CKD, CHD and MI should be <130/80 mm Hg which is the target to be used in this trial. This target is applicable to office measured BP, and the BHS suggest that for home monitoring this target should be adjusted by 10/5 mmHg, resulting in a home measurement target of <120/75 mmHg.

Participants will be trained to self monitor blood pressure using an automated electronic sphygmomanometer and guidelines developed and tested by our group over the last 10 years. They will be asked to measure blood pressure in a seated position with the arm supported on a table or similar so that the cuff is at the level of the heart. Two readings will be required, with a five-minute rest period between them. The second of these readings will be used to determine if medication requires altering. This is because blood pressure decreases on repeated measurement and two measurements have proven to be both acceptable for patients and feasible in the long term with over 90% of individuals in the TASMINH2 trial able to self monitor over a year. Patients will self monitor blood pressure for the first week of each month of the study, and will take measurements in the morning. They will be provided with a simple guideline to colour code readings along the following lines: Red (High) >180/100mmHg, Amber (above target) 121-180/76-100mmHg, Green (normal) 100-120/ ≤75 mmHg, Blue (very low) SBP <100mmHg.

In each week of monitoring, any red or blue readings that persist when a third measurement is taken five minutes after the second reading will require the participants to contact their practice nurse for advice and potentially will need checking. Four or more amber readings on each of two consecutive months will trigger a change in medication. Green (or less than four amber) readings will simply require further monitoring the following month.

**Dissemination of home readings:** Participants will be provided with a simple form to complete each month regarding their blood pressure readings. This requires them to record their daily readings and colour coding for the measurement week to determine any action that is required at the end of the week. Information regarding medication changes required will also be recorded on this form. The form will be printed on three-part non-carbon copy paper (NCR) to allow one copy to be kept by the patient, one to be returned to the research team, and one to be posted to the GP should a medication change be required. Reply paid envelopes will be provided for this purpose. Additionally, at each follow up visit, data from each participant’s individual blood pressure machine will be uploaded on to a computer, so that the research team also has an electronic copy of all the readings. General practices and participants will also be offered copies of this information.

**Self titration of medication:** Each intervention participant will be given an individually tailored three-step self management plan through which to adjust
medication according to measured blood pressure (see guideline document). The choice of medication changes will be decided on by their own GP. Each step will represent a single medication change (additional medication or increased dose) that will be made following two consecutive measurement weeks of four or more amber readings. Three steps means three medication changes, and with a monthly monitoring schedule, an individual would not need to see their GP, regarding their blood pressure, for at least eight months, assuming no red or blue readings. Medication choice will remain at the discretion of the GP who will be provided with an algorithm summarising the national clinical guidelines for advice on hypertension. Any additional monitoring (for instance blood tests or urinalysis) will be the responsibility, and at the discretion, of the GP but the paperwork will be arranged so that this can be incorporated.

When a medication change is required, the participant will be asked to indicate this on their monthly BP measurement form sent to their GP, in order to request the next step of their titration plan. This form will then be used by the practice to issue the prescription, which the participant will collect in the usual manner. This will ensure that GPs are engaged in the titration process throughout the study, and that participants have access to the prescription as they require it.

**Follow up:** Each patient will be in the trial for one year. Follow up by the research team will occur at six months and one year following baseline randomisation. Each follow up visit will be timetabled for no more than one hour. At these follow-up clinics participants will again have their BP and weight measured and will be asked to complete a questionnaire similar to that completed at baseline. The research team will check that the intervention participants are correctly using the blood pressure monitors to measure their blood pressure, upload their home readings and confirm that they are completing their measurement forms, including the open-ended text question (see qualitative section), and medication request forms correctly. Finally, as done at baseline, patients will be given a diary to complete daily for one week to assess lifestyle behaviours and associated self-efficacy. They will be asked to start this on the first Monday of the subsequent month, and to post the completed diary to the research team using a provided freepost envelope. **At the final follow up, as a means of gaining additional feedback about the trial, participants will be given a blank postcard and a freepost envelope and asked to write a few sentences about their experience of the trial. Those in the intervention group will be asked to comment about how they found self management in the context of the trial and those in the control group will be asked to comment on their experience of the trial in general.**

**Withdrawal from trial:** Subjects will be withdrawn from the trial if they choose not to continue, if their GP feels that continued self management or participation in the trial is inappropriate or if they are no longer eligible due to pregnancy, specialist management of blood pressure medication or illness precluding participation. Subjects who withdraw from the intervention will be asked if they are prepared to continue to attend follow up clinics. Experience from previous studies is that many people who decide to stop self monitoring / managing are still prepared to attend follow up. Subjects who choose to withdraw will not be replaced. All patients who attend follow-up visits and have complete data for the primary outcome will be included in the analysis without imputation for missing data.
**Outcome Measures and Measurement**

The primary outcome of the trial will be difference in the reduction of office SBP from baseline to 12 month follow up between intervention and control. This will be measured using a validated automated electronic sphygmomanometer so as to reduce bias potentially introduced by the unblinded nature of the investigation. Six readings will be taken at one-minute intervals and the mean of the 2nd and 3rd reading will be used as the primary outcome.

Secondary outcomes will include: difference in the reduction of office SBP from baseline to 6month follow up between intervention and control, difference in the reduction of office DBP from baseline to 12 month follow up and from baseline to 6 months between intervention and control, percentage time in target BP range, change in pulse rate, change in self-management self-efficacy (adapted Diabetes self efficacy scale \(^{28,32}\)), change in lifestyle behaviours (Dietary Quality Score, \(^{33}\) adapted SLIQ \(^{25}\)), change in health-related quality of life \(^{34}\), change in BP measurement method preference, change in anxiety \(^{35}\), change in attitudes to health and healthcare, \(^{23,24}\) change in use of other self-management strategies \(^{21,22}\), reasons for non-participation, and adverse events. Blood pressure outcomes will be measured in the same manner as the primary outcome, whereas the other secondary outcomes will be assessed using validated questionnaires where appropriate, by collection of original data (weight and height) or extracted data from notes i.e., medical history. Mortality data will also be collected by linkage to the National Register therefore NIGB permission will be sought for this.

**Analysis**

The analysis will consist of a mixed model analysis to examine differences between intervention and control patients in within subject reductions of systolic blood pressure between baseline and twelve months. The primary analysis will include all available subjects, i.e., all of those with complete data from follow up. The primary analysis will be adjusted for practice (as a random effect), baseline blood pressure, gender and high risk group. A sensitivity analysis will examine the potential effect of missing data. This will include multiple imputation, replacement of missing data by the most recent previous data or by the mean of the series. Planned sub group analyses will be of older vs younger (65 as threshold), males vs females, better controlled at baseline vs worse controlled at baseline (threshold 145 systolic), the different risk groups and deprivation. Analyses will be performed at the end of the trial after all data has been collected. No interim analysis will be performed as we do not anticipate that there will be any difference in serious adverse event rates between the two groups, because the study is powered to detect a difference in blood pressure, not end points. Any deviation from the original statistical plan will be described in the final report and publications.

**Economic Analysis**

The economic analysis will be in two distinct parts. The first part is a cost-effectiveness analysis conducted alongside the randomised clinical trial (trial-based
The second part is a model-based cost-effectiveness analysis, building on the trial-based analysis and using published data on long-term outcomes and costs.

a) A trial-based economic evaluation comparing the strategy of self-management of blood pressure in patients with stroke and other high cost conditions to the strategy of usual care will be conducted with a primary outcome expressed in terms of the cost per additional 1 mm Hg reduction in office SBP from baseline to 12 months. Use of utility-based outcomes (EQ5D) will allow a secondary outcome to be the cost per quality-adjusted life year (QALY) gained over the same 12 months period. The results for both outcomes will be expressed in terms of incremental cost-effectiveness ratios (ICERs). The base case economic evaluation will adopt the NHS perspective. NHS costs will be determined for resources used in the trial including hospital and GP consultations, medications, referrals, equipment and training. Data on resources used in the intervention groups (equipment and training) will be collected by the research team. All other resource use data will be collected prospectively by routine practice computer systems and downloaded by the research team at the final follow up visit. Cost data will be derived from sources such as the British National Formulary (BNF), the National Schedule for Reference Costs and the Unit Costs of Health and Social Care (PSSRU).

b) Building on the results of the trial the model-based analysis will estimate the long-term cost-effectiveness of self-management of blood pressure in people with stroke and other high risk conditions in terms of cost per QALY gained. The model type and structure will be informed by reviewing modelling studies undertaken which consider outcomes after stroke and other high risk conditions and experts within the team will advise on the final structure of the model.

Costs to be included in the model are for self management (from the trial based analysis), hospital stay and readmissions and long-term stroke and other risk conditions, costs related to level of disability/quality of life after stroke and other risk conditions and discharge destination. Resource use will be determined from the trial and estimates from the literature. As before, unit costs will be collected from published sources (National Schedule for Reference Costs and the PSSRU). Outcomes will be in the form of survival and quality of life and will use data collected from the trial and literature on quality of life after stroke.

The model will be run over remaining patient lifetime, with costs and benefits discounted at a rate of 3.5%. The analysis will be conducted from an NHS and personal social services perspective. Extensive deterministic sensitivity analysis will be undertaken to assess the impact of changing the values of key parameters. For each important model parameter, we will determine a point estimate and construct a probability distribution around that estimate. Probabilistic sensitivity analyses will be conducted to deal with uncertainty in model parameters and cost-acceptability curves presented.

Qualitative Analysis

This part of the study seeks insights into patients’ actual decision making processes regarding whether to seek professional advice, whether to make a medication change,
or any concerns they may have, and also to explore healthcare professional perspectives on the issues raised.

**Open comments:** Each month, on an open-comment section of their BP measurement record, patients will be asked to write down their description of any action they took and whether it followed protocol or not, their decision making process, and their thoughts and feelings associated with the decision making. This approach is useful for capturing aspects of a patient’s experience of an intervention which may otherwise not be documented. 36 To maximise response, or if the space available on the form is not adequate, patients will also be given the option to return their comments by e-mail or telephone. 37, 38 The open comments will be analysed, with the help of a computer package (SPSS Text Analysis for Surveys™) by content analysis using both quantitative (e.g. number of times a word/phrase mentioned) and qualitative (e.g. examples of participants’ own words to reflect emerging themes) techniques.

**In-depth interviews:** Based on the themes arising from the above a purposive sample of patients and healthcare professionals (up to 20 of each, depending on emerging data) will be selected for sequential interviews throughout the study to further explore particularly interesting and relevant themes arising from the data. Interviews will be carried out in patients’ homes and with healthcare professionals in their GP practice using interview topic prompts. 40 Interviews will be audiotaped and transcribed and constant comparative analysis will be used to interpret the data. 41 40 To maximise theoretical sensitivity, researchers from different disciplinary and professional backgrounds will contribute to the development of the analysis and conceptual framework. 42 Concepts identified will be integrated into themes providing a structure for presentation of findings.

**Non-Participation Analysis**

Included with the letter of invitation to take part in the trial, will be a form for people to voluntarily return should they wish to decline the invitation. This will ask for their reasons for wishing to decline and permission to access their medical records as well as requesting basic demographic details

**Data Handling and Record Keeping**

Data will be recorded onto a combination of electronic and paper case record forms (CRFs). In the case of electronic forms, underlying data will be stored in password protected files with strong patient identifiers kept separately from the rest of the data. Source data will consist of:

- Blood pressure readings
- Pulse rate
- Medical History
- Current medications
- Demographic characteristics
- Height/ weight
- 6 point state anxiety questionnaire 35
- BP measurement method preference
Simple lifestyle indicator questionnaire (adapted SLIQ \textsuperscript{25})
Dietary Quality Score \textsuperscript{43}
Health-related Quality of Life (EQ5-D \textsuperscript{44})
Self-efficacy (adapted diabetes self efficacy scale \textsuperscript{28, 32})
Self-management attributes (Partners in Health Scale \textsuperscript{45})
Attitudes to Health and healthcare \textsuperscript{23 24}
Use of other self-management strategies \textsuperscript{21, 22}
Mortality data from the National Register.

\textit{Direct Access to Source Data/Documents}; The investigators will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents as necessary.

\textit{Quality Control and Quality Assurance}; Data for this trial will be entered onto an electronic database which will have built in safeguards regarding data quality. All research staff and practice staff involved in the study will be subject to quality control checks by the relevant Research Practice Network.

\textit{Maintenance of trial treatment randomisation codes and procedures for breaking codes};
Randomisation codes will be held centrally. The trial is open and so breaking the code for an individual person will not be required.

\textbf{Potential problems with compliance}

Compliance in this study will take a number of forms. Compliance to the protocol with respect to self management for the intervention group will be monitored by auditing the patient measurement and medication change information sheets that each intervention participant will complete each month, and by review of self monitored blood pressures. Compliance to prescribed medication and to non pharmacological interventions will be judged by self report using validated questionnaires.

\textbf{Risks to the safety of participants involved in the trial}

It is anticipated that the potential risks of this study are low and similar to those associated with usual care. Particular issues are when a patient finds an excessively high (above 180 mmHg systolic) or low blood (below 100 systolic) pressure reading whilst conducting home monitoring. The patient guideline will advise contact with the supervising physician or nurse in such cases for a blood pressure check and further management if required. Training of participants will cover repeated measurements in the case of high or low readings and a helpline will be available should participants or clinical staff require advice over and above that provided in the guideline. Prescription of all medication within the study will remain under the control of the participants GP who will make changes to prescriptions as required. Patients will be given specific advice to attend their GPs should they experience an adverse event thought to be due to their medication. It is possible that blood pressure monitoring and
self titration may increase anxiety in some participants but previous work by the team, specifically in the TASMINH and TASMINH2 trials, has not found this to be common. However, should an individual feel excessively anxious they will be free to withdraw at any time.

*Procedures for eliciting reports of and for recording and reporting adverse events and intercurrent illnesses*

Patients experiencing adverse events will be asked to contact their own primary care physician as appropriate. All such contacts will be recorded. Where contact is made with the patients’ own primary care physician, details will be requested and/or extracted from the medical records at follow-up. Additional advice will be available via the study team for participants who are unclear as to appropriate action.

**Ethical Issues**

The main ethical issues relating to this trial are confidentiality and data protection. Initial invitations will be sent by the practices and subsequent data held with consent. All of the research team with access to patient identifiable data will have honorary contracts with the relevant practices and letters of access from the primary care organisations. All participating patients will be asked for permission to gain access to the medical records. All patients will undergo a consenting process with a member of the research team before taking part in the study. The research project will be registered with the Data Protection Commissioner via the University of Birmingham Data Protection Officer.

**Trial Management**

Day to day management
The study will be managed on a day to day basis by Dr Emma Bray supervised by Prof RJ McManus.

Responsibilities of Team Members

Prof RJ McManus: Chief Investigator; Overall responsibility for the study
Dr Emma Bray: Trial Manager
Dr Miren Jones: Qualitative Research Fellow
Dr Christina Penaloza/ Dr Billingsley Kaambwa: Health economists
Mrs Amanda Davies: Trial Secretary
Research Nurses: Research Clinics

Trial statistician

Mr Roger Holder

Trial Steering Group
Financing and Insurance

The trial is funded by a NIHR programme grant, a NIHR national school primary care trial development grant, and by a NIHR career development fellowship award to Prof RJ McManus, the chief investigator. Trial insurance to cover negligent harm will be provided by the sponsors of the trial, the University of Birmingham. Individual medical indemnity insurance (typically by the MDU or MPS) will cover negligent harm arising from clinical care provided by participating primary care physicians. No funding is available for non negligent harm.

Publication Policy

The results from this study will be published in a peer reviewed journal. This publication and the data on which it will be based will remain independent of the funders.

Reference List


37. Selwyn N, Robson K. Using e-mail as a research tool. *Social research update* 21 1998;

38. Meho L. E-mail interviewing in qualitative research: a methodological discussion. *Journal of the American Society for Information Science and Technology* 2006;57:1284-1295.


