ARTICLE TITLE

A Phase IV, Multi-Centred, Open Label, Randomised Study Assessing the Cardiovascular Outcomes Following Treatment of White Coat Hypertension with Established Anti-Hypertensive Drugs versus Standard of Care in the Very Elderly – Feasibility Study

Running Title:

Outcome of the HYVET 2 feasibility study

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ABSTRACT

Background:

Cardiovascular disease remains an important global cause of morbidity and mortality and hypertension is a major contributing risk factor, particularly in older people. There has been controversy regarding the appropriateness of treatment of white coat (WCH) hypertension in older people. NICE guidelines for the diagnosis and treatment of hypertension recommend the widespread use of ambulatory blood pressure monitoring (ABPM) in order to exclude the presence of WCH, as the benefits of treatment are unproven.

Aim:

To determine whether the treatment of WCH in the very elderly is feasible and outweighs any adverse events.

Methods:

GP practices identified potentially eligible participants who were invited to attend a clinic where informed consent was received and screening tests carried out. Successful screening would lead to randomisation between either (a) the treatment arm with established antihypertensive drugs (Indapamide MR and Perindopril Erbumine) or (b) the no treatment arm which is current standard clinical care.

Findings:

Participant identification was solely achieved by conducting searches of electronic patient records. One hundred and four potential participants were approached of which 10 consented to take part in the study. Of these 10 none were deemed eligible for randomisation from the screening tests.

Conclusion:

The HYVET 2 study has shown that a clinical trial of antihypertensive drugs for the treatment of WCH in the over seventy-five-year-old population is difficult to recruit. The methodology used is not feasible and hence the recruitment was not successful.

Keywords:

White Coat Hypertension, Cardiovascular Disease, Anti-Hypertensive Drugs, Feasibility

Trial Registration: ISRCTN 13127656 (https://www.isrctn.com/ISRCTN13127656)

INTRODUCTION

Cardiovascular disease (mainly stroke and coronary artery disease) remains an important global cause of morbidity and mortality and hypertension is a major contributing risk factor, particularly in older people (1). The overall prevalence of hypertension in all adults in England is 28.6% and this compares with a prevalence of 65.6% in patients over 75 years of age (2). With an ageing population and the greatest expansion in population expected in the over 65 age group, hypertension will become a more prominent treatable and preventable cause of premature death (3).

There has been controversy regarding the appropriateness of treatment of hypertension in older people based on data from epidemiological studies, which suggest that there is a higher risk of death in patients over 80 years of age with lower Blood Pressure (BP) (4-6). This notion has been challenged by data from the HYpertension in the Very Elderly Trial (HYVET) which showed that antihypertensive treatment in persons 80 years or older is beneficial (7). As a result, NICE guidelines recommend BP control to reduce cardiovascular risk, irrespective of the age of the patient (8).

Current NICE guidelines for the diagnosis and treatment of hypertension recommend the widespread use of ambulatory blood pressure monitoring (ABPM) in order to exclude the presence of WCH, as the benefits of treatment are unproven (8). WCH is defined as persistently raised clinic blood pressure readings (>140/90 mmHg) in individuals who have normal home or ABPM readings (<135/85 mmHg) and may affect up to 30% of the population, according to some studies (8). Interestingly, up to 42% of patients who have WCH go on to develop sustained hypertension (9). Evidence for a role for the active treatment of WCH has been contentious as some research studies do not support protection against cardiovascular events

(10, 11). However, a study by Franklin et al. suggests that men and diabetics with untreated WCH are at increased risk (12). Furthermore, the HYVET ambulatory blood pressure sub-study analysis estimates that 50% of patients in the main study may have had WCH (13). It is therefore as yet unknown whether the patients with WCH benefit from treatment. The feasibility study reported here was carried out to serve as a prelude to a definitive randomised controlled trial, in order to determine whether the treatment of WCH in the very elderly is feasible and outweighs any adverse events.

METHODS

The CONSORT flowchart is shown in Appendix 1.

Objective and Outcomes

The HYVET 2 feasibility study was established to focus on the following outcomes:

Objectives	**Outcome Measures**
Estimate the proportion of eligible patients that can be recruited from initial screening	Review of Screening Logs Proportion of screened patients eligible for recruitment
Explore different methods of identifying/recruiting patients	Search and mail out, opportunistic recruitment and posters/adverts are included in the protocol design
Ascertain the willingness of GPs to recruit and randomise patients	Feedback from Primary Care team and GPs directly
Ascertain the willingness of patients to be randomised	Review of Screening Logs Proportion of patients eligible that agree to be randomised
Estimate the recruitment rate	Rate of recruitment over trial duration Proportion of patients eligible that provide consent
Assess adherence to the treatment protocol	Pill count
Monitor withdrawal from the clinical trial	Proportion withdrawing and reason for withdrawal
Expand the opportunities for PPI (patient and public involvement) in the research design and its subsequent conduct and dissemination	A lay member will sit on the TSC. A PPI panel will review patient facing documents
Estimate the incidence of Cardiovascular Events	Composite of cardiovascular events
Measure ambulatory and home blood pressure	Blood pressure (mm Hg)

Evidence of feasibility was defined as 20% of eligible patients approached being recruited, recruitment rate of 1 patient per practice every two months and at least 50% of the patients completing the study. For each participant, at least 80% of data should be complete at each time point.

Participants and screening

The study was run from 30 GP Practices across England and supported by the Primary Care Clinical Research Network (LCRN). GP practices identified potentially suitable participants ≥75 years old using appropriate clinic resources such as database searches and clinic records. In addition to search and mail out, opportunistic recruitment was also possible during routine appointments.

Potential participants who accepted the invitation to take part in the study were invited to their practice to provide informed consent and have screening assessments which included past and present medical history, social history, current medication and treatment for hypertension within the previous six months; Montreal Cognitive Assessment (MoCA) Mental State Examination (<22); non fasting biochemistry bloods and haematology; urinalysis; HbA1c test; Height and weight; a 12 lead ECG and clinic blood pressure. Participants with a mean sitting clinic systolic BP ≥150mmHg but <200mmHg and diastolic BP <110mmHg were offered a 24-hour Ambulatory Blood Pressure Machine (ABPM) or Home Blood Pressure Machine (HBPM) to record home blood pressure in the week prior to their next clinic appointment.

Baseline assessments and randomisation would have followed fulfillment of the screening requirements.

Assessments, randomisation, intervention and blinding

Baseline assessments included frailty assessments (ROCKWOOD and PRISM-7), Barthel index, current medical conditions, concomitant medications, clinic blood pressure, HBPM (for all participants), patient diary checks if applicable and adverse reaction recording and reporting. A mean awake ambulatory systolic BP is <135 mmHg and mean awake ambulatory diastolic BP is <85mmHg (from at least 14 measurements) or for HBPM from BP readings twice a day for at least 5 days was used to confirm WCH which would have allowed participants to be randomised. A concealed, 1:1 allocation ratio between either (a) the treatment arm with established antihypertensive drugs (Indapamide MR and Perindopril Erbumine) or (b) the no treatment arm which is current standard clinical care was generated using the web-based system 'Sealed Envelope' (https://www.sealedenvelope.com/). This was an open label study.

Six follow up visits and an end of study visit were planned to assess MoCA Mental State Examination, Frailty Assessment (ROCKWOOD and PRISM-7), Barthel Index, Current medical conditions, Concomitant Medications, Clinic Blood Pressure, HBPM (all participants), Biochemistry bloods, Haematology bloods, Urinalysis dipstick, HbA1c test, Weight, 12 lead ECG, Patient diary checks, Adverse Event Recording & Reporting, Assessment of any falls since the last visit, IMP adherence checks (pill count for intervention arm only), Medication review (intervention arm only), Prescription (intervention arm only), Referral back to GP for standard ongoing care. Post Treatment Follow Up was also planned for two years after participants stopped treatment. Follow up information would have been gathered from the GP records for each participant, where available, including whether the participant is alive or deceased and whether any cardiovascular outcomes have occurred.

Statistical Analysis

Simple descriptive statistics are presented for age, gender and ethnicity. No further analysis was possible.

RESULTS

Recruitment and Retention

The intended sample size of the study was for 100 participants to be randomised after having been confirmed with WCH based on ABPM or HBPM. One hundred and four potentially eligible participants were approached by their GP practice to take part in the study. Ten (9.6%) of these provided informed consent and underwent screening assessments; however, all were excluded as screening failures and nobody was randomised.

Of those patients who were identified as being potentially eligible and were approached (n=104) there was no contact or response from 39 patients (37.5%). The impact of the study on the patient; for example, number of clinic visits, was the reason for 15 (14.4%) people declining to take part. Potential participants not wanting more medication was cited by 8 (7.7%) patients. Other reasons for patients not taking part were the patient was not interested (5 (4.8%)); the patients expressed interest but did not have a screening visit (9 (8.7%)); 2 (1.9%) patients were found to be ineligible before the screening/consent visit; 10 (9.6%) declined to

provide a reason; multiple reasons were given by 4 (3.8%) patients and the study ended before 2 (1.9%) patients were able to have a screening visit.

Of the 10 patients who were screened five were ineligible as their clinic blood pressure did not meet the protocol threshold; one had a clinic blood pressure deemed in need of medication; one had an ABPM that did not pass the threshold; two had MOCA scores <22 and one did not complete screening as the study ended.

Practices reported the eligibility criteria significantly limited the output of their searches meaning many practices were left with only a few people to approach from their entire patient population. In addition, some practices reported many potentially eligible patients in their practice population were already taking antihypertensive or contraindicated medication so were screened out of searches.

Demographics

The mean age at the point of consent was 79.8 years (SD 4.04). Six were female and four were male. All 10 participants were of white ethnicity.

Assessment of feasibility

Against the earlier defined criteria against which to judge feasibility, the study conclusion is that a definitive trial of this design is unfeasible. The study failed to recruit any participants to the point of randomisation meaning assessment of most of the study objectives cannot be made.

DISCUSSION

Through discussion with principal investigators at sites and receipt of screening and enrolment logs it became apparent that identification of potential participants was entirely achieved by creating and running searches of practice electronic patient record systems. It was also highlighted that ABPM is not a term that can be searched on the electronic patient records and output from these searches depends on the quality and consistency of data input. Once a practice had exhausted this avenue of identifying people to approach they rarely found new potential participants by repeating searches.

The majority of practices that were activated remained engaged and keen to deliver the study. Many practices also reported limited resources available for research which combined with a study requiring numerous clinic visits and tests could have made the study less attractive to some sites that initially expressed interest in running the study but subsequently declined.

In addition, we found that we used strict eligibility criteria. This was felt to be important as we were dealing with highly vulnerable patients who may already be on a number of medications due to their age. However, we found that this was a barrier to recruitment. In addition, during the period of recruitment of the trial there has been an increased awareness of polypharmacy and side-effects in the elderly. This will probably have contributed to the potential participants not being keen to join as taking another medication would not have been desirable.

CONCLUSION

The HYVET 2 study has shown that a clinical trial of Indapamide MR and Perindopril in the over seventy-five-year-old patients involving many clinic visits and procedures was not feasible with the current employed methodology. The reasons given above indicate that, despite limited research resources in some cases, practices remained engaged and keen to make the study work, but the study was not attractive enough to potential participants. For those patients who did consent, the screening and eligibility criteria were such that nobody was randomised. With permission from Dunhill Medical Trust (funder) a separate study was developed to look in more depth into the reasons HYVET 2 struggled to recruit. This study will be reported separately.

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Conflict of interest statement:

There are no conflicts of interest to declare.

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APPENDIX 1

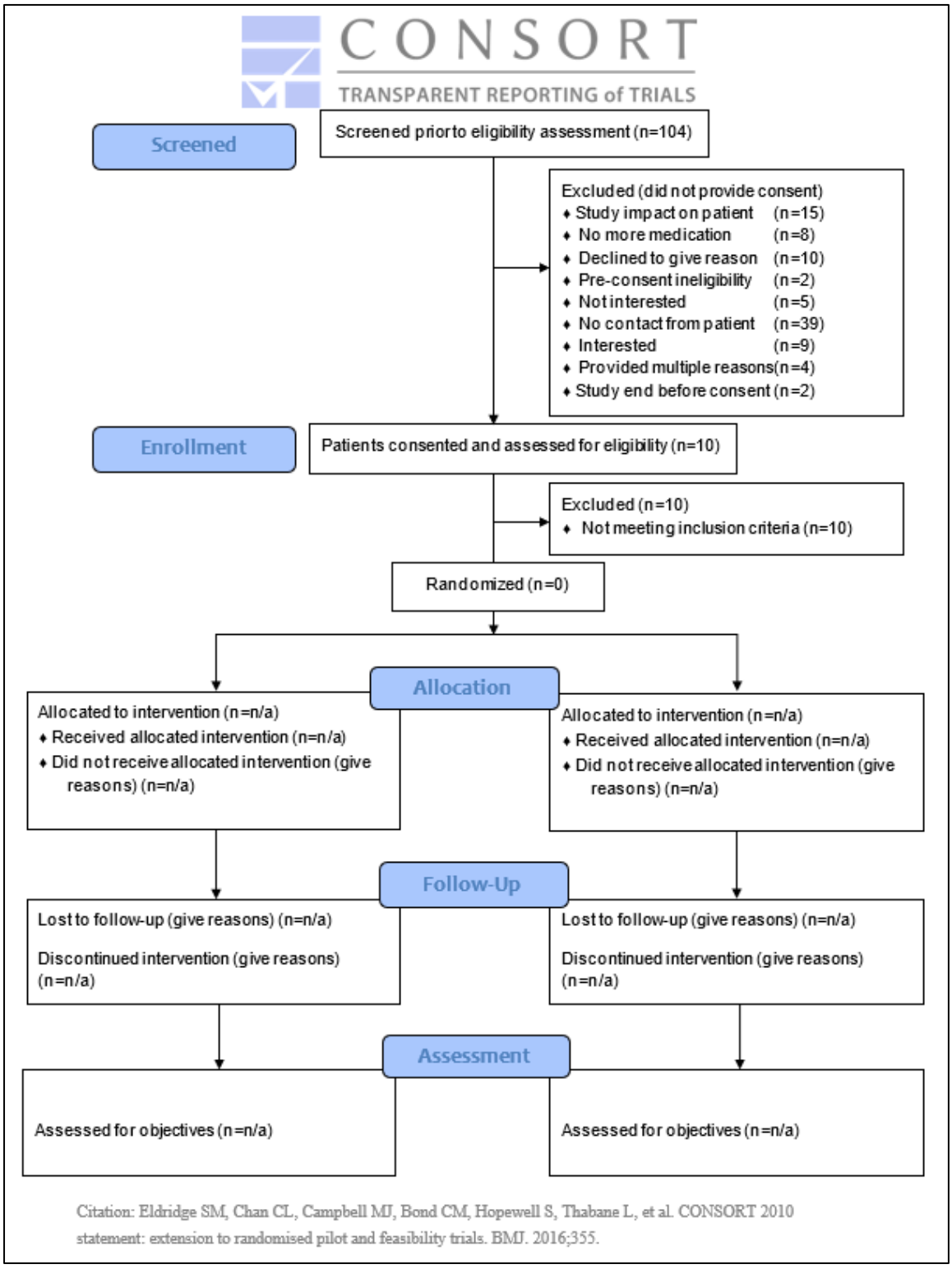

Figure 1. CONSORT flow diagram, extension to randomised pilot and feasibility trials.