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Hypertension in the Very Elderly Trial (HYVET)

Protocol for the Main Trial

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Abstract

A number of trials and meta-analyses have demonstrated clear benefits of blood pressure (BP) reduction in patients aged <80 years with regard to the reduction in stroke and cardiovascular events. However, a variety of studies have suggested that the positive relationship between BP and cardiovascular mortality is weakened or indeed reversed in the very elderly. Most intervention trials to date have either excluded or not recruited sufficient patients aged ≥80 years to determine whether there is a significant benefit from treatment in this age group. A meta-analysis of intervention trials that recruited patients aged ≥80 years has suggested a benefit in terms of stroke reduction but has also raised the possibility of an increase in total mortality. The benefit to risk ratio therefore needs to be clearly established before recommendations can be made for treating very elderly patients with hypertension.

The Hypertension in the Very Elderly Trial (HYVET) pilot recruited 1283 patients aged ≥80 years and showed the feasibility of performing such a trial in this age group. It was a Prospective Randomised Open Blinded End-Points (PROBE) design but the main trial has additional pharmaceutical sponsorship to run a double-blind trial. Therefore, the main trial is a randomised, double-blind, placebo-controlled trial designed to assess the benefits of treating very elderly

patients with hypertension. It compares placebo with a low dose diuretic (indapamide sustained release 1.5mg daily) and additional ACE inhibitor (perindopril) therapy if required.

As in the pilot trial, the primary end-point is stroke events (fatal and non-fatal) and the trial is designed to determine whether or not a 35% difference occurs between placebo and active treatment. The main objective will be achieved with 90% power at the 1% level of significance. Secondary outcome measures will include total mortality, cardiovascular mortality, cardiac mortality, stroke mortality and skeletal fracture.

2100 patients aged ≥80 years are to be recruited and followed up for an average of 5 years. Entry BP criteria after 2 months of a single-blind placebo run-in period are a sustained sitting systolic BP (SBP) of 160 to 199mm Hg and a diastolic BP of 90 to 109mm Hg. The standing SBP must be >140mm Hg. The trial will be carried out in accordance with the principles of Good Clinical Practice. We describe in detail the protocol for the main trial and discuss the reasons for the changes from the pilot, the use of the drug regimen, and the BP criteria to be used in the trial.

The benefits of treatment of patients with hypertension up to the age of 79 years with regards to the reduction in stroke and cardiovascular events have been well documented by several trials and meta-analyses over the last 15 years.[1-9] However, most of these trials have either excluded patients aged ≥80 years or recruited too few to establish the benefit to risk ratio in the very elderly.

The Medical Research Council trial in the elderly[1] and the Hypertension in Elderly Patients in primary care trial[2] excluded patients over the ages of 75 and 80 years, respectively. The European Working Party on high BP in the elderly trial (EWPHE)[3] recruited patients of any age over 60 years, but only 155 patients out of the 840 recruited were ≥80 years. No benefit from treatment was shown in patients in the group aged ≥80 years. The Swedish trial in Old Patients with Hypertension (STOP-Hypertension)[4] recruited patients aged 70 to 84 years of age and of the 1627 patients recruited 269 were aged ≥80 years. Again, no benefit from treatment was demonstrated in the patients in the ≥80 years' age group.

In trials recruiting elderly patients with isolated systolic hypertension (ISH) larger numbers aged ≥80 years were recruited. In the Systolic Hypertension in the Elderly Program trial (SHEP)[5] there was a 45% reduction in stroke incidence but no decrease in fatal events in those who were in the group of patients aged ≥80 years. In the Systolic Hypertension in Europe trial (Syst-Eur),[6] in which the results were broken into 3 age strata (60 to 69, 70 to 79 and ≥80 years) the benefits of active treatment were present for combined fatal and non-fatal end-points in patients aged ≥80 years, but were absent for total and cardiovascular mortality.

In patients aged ≥80 years of age, epidemiological data suggest that those with a higher BP have a better survival rate.[10-12] This is probably because those with a lower BP may have other confounding reasons which result in them having a lower BP and a reduced survival.[12] Such conditions include cardiac disease, dementia and cancer.

Recently a meta-analysis of patients aged ≥80 years who were recruited to double-blind intervention trials[13] reported a significant reduction of 36% in fatal and non-fatal strokes, 23% in all cardiovascular events and 42% in heart failure. However, there was no treatment benefit for cardiovascular death and more importantly there was a 14% [95% confidence interval (CI) 0 to 31; p = 0.05] relative excess of death from all causes. The authors pointed out that the positive results were not robust as addition of data from only 1 large hypothetical trial of proper design with no treatment effect would be enough to make the results nonsig-

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nificant. This meta-analysis suggests that in treating the very elderly there may be a balance between reducing the risk of a cardiovascular event and increasing mortality.

Thus, as stated in the 1999 World Health Organization – International Society of Hypertension guidelines for the management of hypertension, 'there is uncertainty about the value of antihypertensive treatment for patients over the age of 80 years.'[14] Linked to this is the fact that within the elderly the fastest growing section is people aged >80 years who consume a significant amount of health and social care services. Hypertension is common in individuals aged ≥80 years with 50% of women in this age group having a casual systolic blood pressure (SBP) over 160mm Hg. Health and social care planners require evidence for the benefit of treating this age group as the numbers requiring treatment may be large, although potential savings in stroke reduction and the costs of stroke care may also be significant. There is a need for a well conducted adequately powered trial to address this question.

The Hypertension in the Very Elderly Trial (HYVET) is designed to establish the benefits and risks of treating patients with hypertension who are aged ≥80 years. A pilot trial has been conducted which recruited 1283 patients. The pilot trial was funded by the British Heart Foundation and financial support for the manufacture, labelling and distribution of drugs was not available. An open design was therefore employed with end-points being assessed by a blinded end-point committee.[15] This design is referred to as a Prospective Randomised Open Blinded-End-point (PROBE) design. The pilot trial had 3 treatment groups: (i) no treatment; (ii) treatment based on a low-dose diuretic (usually bendrofluazide 2.5mg or hydrochlorothiazide 25mg); and (iii) treatment based on an angiotensin-converting enzyme (ACE) inhibitor (usually lisinopril 5mg or enalapril 10mg). The pilot trial tested the randomisation procedures, completion of record forms, adherence to eligibility criteria, quality of the data, methods of determining outcome, different methods of data entry and the protocol in general. It also developed a network of centres capable of recruiting significant numbers of patient with hypertension who are aged ≥80 years as well as showing the feasibility of performing such a trial in this very elderly age group.

After the start of the pilot trial, financial support from the pharmaceutical industry (Institut de Recherches Internationales Servier) was secured which has allowed the Steering Committee to change the design of the main trial to a placebo-controlled, double-blind trial.

1. Trial Design

The main objective of the trial is to investigate the prevention of fatal and non-fatal strokes, namely to determine whether or not a 35% difference in stroke events (fatal plus non-fatal) occurs between placebo and active treatment in patients with hypertension who are aged ≥80 years. This is comparable with the results from intervention trials in the younger elderly: a reduction of 36% [odds ratio (OR) 0.64, 95% CI 0.55 to 0.73] in trials of elderly patients with hypertension[9] and a reduction of 30% (OR 0.7, 95% CI 0.60 to 0.72) in trials of ISH in the elderly.[16] The total number of patients required will be 2100 followed for 5 years for 90% power and 1% level of significance. It is expected that the placebo rate for non-fatal and fatal stroke events will be 40/1000 patient years.

The secondary objectives that will be achieved with this number of patients, 80% power and 5% significance level are the detection of:

- an 18% difference in total mortality (expected placebo rate 80/1000 patient years);
- a 25% difference in cardiovascular mortality (expected placebo rate 40/1000 patient years);
- a 39% difference in cardiac mortality (expected placebo rate 16/1000 patient years);
- a 48% difference in stroke mortality (expected placebo rate 10/1000 patient years);
- a 21% difference in skeletal fracture rate (expected placebo rate 60/1000 patient years).

Other objectives of the trial will be to assess the incidence of retinal lesions, overt heart failure, renal failure, dissecting aortic aneurysm and acute

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myocardial infarction (MI) and the effect of treatment in this patient population.

Thus, the main trial is a randomised double-blind, placebo-controlled trial. Unlike the pilot trial there will be only 2 groups, placebo and active treatment and patients will undergo a 2-month placebo run-in phase to establish that patients have sustained elevated levels of BP. During the run-in period any active antihypertensive treatment will be stopped and 1 placebo tablet will be given matching the initial active treatment. The patients will have their BP measured in the sitting position after at least 1 month of placebo (i.e. the patients second visit) and again after at least another month. The sitting BP will be taken twice after sitting for 5 minutes and, on the third visit and thereafter, the standing BP must be taken twice after standing for 2 minutes. An average SBP ≥200mm Hg excludes the patient as does a diastolic blood pressure (DBP) >109mm Hg (see inclusion criteria).

The standard guidelines of the British Hypertension Society will be followed to ensure proper training, adequate cuff size, appropriate rate of deflation and no digit preference.[17] Standard mercury sphygmomanometers or validated automatic machines will be employed. Phase V diastolic readings will be measured, although when phase V is less than 40mm Hg, phase IV may be utilised in the absence of aortic incompetence.

1.1 Inclusion Criteria

The inclusion criteria are as follows:

- men or women aged ≥80 years at time of randomisation. There is no upper age limit. To ensure that the patients are aged ≥80 years their date of birth will need to be confirmed by an official national document, a copy of which will be kept in the source documents;
- the mean of 2 sitting SBP readings taken on 2 separate occasions 1 month apart (the average of 2 sets of duplicate readings; the first after at least 1 month of the placebo run-in phase) must be 160 to 199mm Hg. Standing SBP must be ≥140mm Hg at the last visit prior to randomisation;
- similarly the sitting DBP must be 90 to 109mm Hg (phase V);
- all ethnic groups are eligible for inclusion in the trial;
- the provision of written informed consent before the placebo run-in phase.

1.2 Exclusion Criteria

The exclusion criteria are:

- known accelerated hypertension (retinal haemorrhages, exudates or papilloedema);
- overt clinical congestive heart failure (CHF) requiring treatment with a diuretic or ACE inhibitor. Patients are accepted if treated with digoxin only;
- renal failure (serum creatinine level >150 μmol/L);
- previous documented cerebral or subarachnoid haemorrhage in the last 6 months (do not exclude patients with ischaemic cerebral and cardiac events, although they must be neurologically and cardiologically stable);
- condition expected to severely limit survival, e.g. terminal illness;
- known secondary hypertension (e.g. renal artery stenosis, chronic renal insufficiency or endocrine origin);
- gout, in the opinion of the investigator;
- clinical diagnosis of dementia;
- resident in a nursing home i.e. where the dependency and care requirements of the patients are such that they require the regular input of qualified nurses and therefore the majority of staff in the home are nurses (other forms of residential care acceptable);
- contraindication to trial medication [e.g. serum potassium level <3.5 mmol/L (indapamide) or >5.5 mmol/L (perindopril)];
- inability to stand up or walk.

1.3 Randomisation

Patient randomisation will be initiated at the coordinating office at the Hammersmith campus of the Imperial College School of Medicine (ICSM) in London on receipt of the completed entry form.

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Patients will be stratified into 4 groups on the basis of sex and age (i.e. 80 to 89 years and ≥90 years). Restricted randomisation will be employed to ensure equal allocation per group within each large centre. An interactive voice response system (IVRS) is employed to tell the investigator which 6-month drug pack to prescribe. The IVRS is a telephone system that allows investigators and the coordinating centre to interact in their native languages with a central patient database.

When a patient is entered into the placebo run-in phase the investigator makes a telephone call to the IVRS and inputs the patients initials, date of birth and date of visit. The coordinating office is informed in order to keep track of the number of patients screened. When the coordinating centre has received the entry form on a patient and checked that they are eligible, they inform the IVRS to permit randomisation according to schedule. The IVRS automatically, in real-time, faxes the centre to inform them that their patient is eligible to enter the trial and that the local investigator can make a call to the system to receive the number of the treatment pack that their patient is to receive.

1.4 Treatment Groups

The goal BP is a sitting SBP <150mm Hg and a sitting DBP <80mm Hg. Treatment will be increased in 2 steps, if necessary, to achieve goal pressures. The timing of the increments is at the discretion of the investigator. Sitting SBP ≥150mm Hg is acceptable if standing SBP is <120mm Hg.

The treatment steps for Group 1 (placebo) are as follows:

1. Placebo indapamide sustained release (SR).
2. Placebo indapamide SR + 1 placebo perindopril (2mg equivalent).
3. Placebo indapamide SR + 2 placebo perindopril (4mg equivalent).

The treatment steps for Group 2 (diuretic ± ACE inhibitor) are as follows:

1. Indapamide SR 1.5mg.
2. Indapamide SR 1.5mg + 1 perindopril 2mg tablet daily.
3. Indapamide SR 1.5mg + 2 perindopril 2mg tablets daily.

The first dose of perindopril or matching placebo will be taken at night. Although patients are very elderly, severe first dose hypotension is not expected because they do not have clinical heart failure needing treatment and are hypertensive when standing. Furthermore, perindopril is relatively free of the first dose effect.[18,19] Should patients be intolerant of indapamide SR 1.5mg they may receive perindopril alone either at the 2mg or 4mg dose depending on their BP response. BP exceeding 209mm Hg systolic or 109mm Hg diastolic despite step 3 titration will be a reason for withdrawal (see withdrawal criteria). The active drugs and matching placebos will be supplied and distributed by Les Laboratoires Servier Industries. There will be a central production site and within each country there will be a supply centre for storing the drugs to ensure the active drugs and placebos are always maintained at an adequate level in each centre. Servier continuously monitor the content of 'treatments' to exclude medication errors. They comply with the standards of Good Manufacturing Practice.

2. Data to be Collected

The case report forms to be used have been designed to collect a reasonable amount of data without being too time consuming for investigators to complete.

The trial entry form will collect data on sitting BP levels from the 2 occasions and standing BP on 1 occasion (systolic and phase V diastolic), as well as sitting heart rate on 1 occasion, weight and height. Details of treatment stopped within last 6 months, current treatment (including noncardiovascular drugs) and details of previous stroke, MI, skeletal fracture and major diseases before randomisation (diabetes mellitus, cancer, etc.) will also be noted. A 12-lead electrocardiogram (ECG) taken within the last 3 months will be requested and a copy is to be sent to the coordinating centre. Current smoking habits, current alcohol intake, type of accommodation and a short assessment of activi-

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ties of daily living are recorded. All patients will have an Orientation Memory Concentration test[20] performed with the addition of the Mini-Mental State Examination (MMSE).[21] Finally, a record of severe adverse effects with placebo and a biochemical screen will be recorded which must include serum creatinine, potassium, sodium, urate (uric acid), blood sugar, total cholesterol and high density lipoprotein-cholesterol levels and the presence or absence of dipstick positive proteinuria.

Patients will be followed up at 3-monthly intervals in the first year of follow-up and thereafter 6 monthly. At each annual visit there will be an assessment which will include many of the items on the entry form including the biochemical screen and ECG. At the intermediate visits only a short report will be required. Biochemical screening is also performed 6 weeks after randomisation and within 6 weeks of starting step 2 medication.

Separate forms are completed for serious adverse events or terminating events. To ensure that data about cardiovascular events that do not lead to withdrawal are recorded there is a separate form for these. It is important to note that even after a non-fatal end-point leading to withdrawal, patients continue to be followed up with the same schedule of visits as in the double-blind phase. This is also true of patients withdrawn from the trial for other reasons. When this is not possible investigators will be asked to provide annual information as to the well-being of the patient. This allows a full intention-to-treat (ITT) analysis. To help in the follow-up of patients, they will be registered where possible with national authorities so that any deaths will be notified to the local investigators, even when the patient has been 'lost' to follow-up.

3. End-Points

All end-points will be assessed by the End-Points Committee who will be blinded to the treatment that the patient received. Clinical and radiological evidence must be supplied by the investigator to support all diagnoses. Additional data will be sought from investigators as required and the monitors (see quality control in section 4) will check all the source documents relating to end-points. Non-fatal events may lead to withdrawal from 'per-protocol (on randomised) treatment' but not from ITT follow-up. Events will be coded using the International Classification of Diseases version 10 (ICD-10).[22]

3.1 Non-Fatal Events Leading to Withdrawal from Per-Protocol Follow-Up

1. Stroke (ICD-10 Code: I60–I64): an acute disturbance of focal (or global) cerebral function with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than vascular. This definition includes complete stroke as well as reversible ischaemic neurological deficit. The latter is defined as an acute disturbance of focal neurological function with symptoms lasting more that 24 hours.

The definition of a stroke does not include a transient ischaemic attack (TIA) [ICD-10 Code: G45]. Although this is recorded during the course of the trial, it is not a cardiovascular outcome event. TIA is defined as an acute disturbance of focal neurological function with symptoms lasting less than 24 hours and thought to be related to vascular disease; these symptoms may include sensory defects, motor defects, amaurosis fugax, cortical blindness, hemianopsia or speech disorders. The severity of stroke will also be detailed using Activities of Daily Living (ADL) and grade of Disability.[23]

2. Incident retinal lesions: exudates, haemorrhage, or papilloedema.

3. Overt heart failure: heart failure requiring treatment with a diuretic, ACE inhibitor or vasodilator for more than 3 months will lead to withdrawal from the trial. An isolated sign or symptom such as swollen ankles or mild dyspnoea should not lead to withdrawal.

4. Dissecting thoracic or abdominal aortic aneurysm.

5. A doubling of the patient's baseline serum creatinine level.

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3.2 Fatal Events

Sudden death, cause unknown (ICD-10 Code: R96): any death of unknown cause occurring instantly (R96.0) or within an estimated 24 hours after the onset of acute symptoms or signs (R96.1). Sudden death also includes unattended death (R98), where the body of the deceased was found and no cause could be discovered. By contrast, unattended death, where a cause is revealed by a postmortem or other convincing evidence, is classified according to the underlying cause of death.

3.3 End-Points Not Leading to Withdrawal From Per-Protocol Follow-Up

3.3.1 Acute Myocardial Infarction

For the diagnosis of acute MI (ICD-10 Code: I21), at least 2 of the 3 following criteria must be met:

1. The patient has a history of retrosternal pain with or without radiation to the shoulder, arms, jaws or abdomen. Pain should last for at least 30 minutes, and not respond to nitroglycerine during the attack.
2. Electrocardiographic abnormalities indicative of MI (Minnesota Code numbers 1-2-1, 1-2-2, 1-2-3, 1-2-6, 1-3-1 through 1-3-6, 2-4, 4-0, 4-1, 5-1) are observed. A diagnosis of silent MI will be made when during the study electrocardiographic changes develop which denote definite MI (Minnesota Code numbers 1-1-1 through 1-1-7, 1-2-4, 1-2-5, 1-2-7, and 1-2-8), even without clinical symptoms or biochemical abnormalities.
3. Biochemical markers of cardiac damage are present. Traditionally, changes in the enzymes creatine phosphokinase (CPK), aspartate transaminase (AST) and lactate dehydrogenase (LDH) are required and are still used in many centres. Peak levels of CPK and AST must be observed within 72 hours after the onset of clinical symptoms, and LDH must peak within 14 days. Preferably, AST and LDH levels should be elevated to twice the upper limit of normal or above. More recently creatinine kinase-MB isoenzyme (CK-MB), CK-MB mass, troponin I and troponin T are being used. Peak levels of CK-MB are 24 to 36 hours, troponin T 10 to 14 days and troponin I 4 to 7 days. These markers provide the additional benefit of stratifying the risk of adverse events.

Investigators who routinely give β-blockers or ACE inhibitors to those aged ≥80 years post-MI will withdraw the patient from per-protocol (on randomised treatment) follow-up, assuming the patient remains on the treatment for 3 months.

3.3.2 Skeletal Fracture

Femoral neck fractures, wrist fracture and other fractures are to be recorded throughout the trial. They will need to be documented with details of operation or x-ray reports on the radiology.

4. Quality Control

The coordinating office and investigators will follow the principles of Good Clinical Practice. This includes the concept that trial information will be recorded, handled and stored in such a way as to allow its accurate reporting and interpretation. A monitoring system has been set up to check on vital source documents (e.g. consent forms, verification of age, etc.) and a random selection of important points relating to the trial protocol.

National initiation meetings will be organised for the investigators which will be attended by members of the coordinating centre staff or the Data Monitoring Committee and the monitor for that particular country. Prior to setting up a centre the monitor will visit the site and facilities where the trial will take place to ensure knowledge of and agreement with the protocol requirements. During the trial the monitors will visit the centres at regular intervals, depending on the recruitment rate and as arranged with the investigator. All information dealt with during these visits will be treated as strictly confidential.

Members of the coordinating centre staff or the Data Monitoring Committee may also visit centres to interview investigators with regard to completeness of data with checks against source documents, recruitment and completion of the log book, digit preference, attainment of goal BP and titration of treatment. These procedures will be also be applied at off-site meetings of investigators. The members of the Data Monitoring Committee and the Ethics

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Committee are not investigators in the trial. The HYVET main trial is thought to be one of the first, long term mortality/morbidity trials to be conducted to Good Clinical Practice standards.

5. Analyses

As previously stated, the total number of patients required for the 2 treatment groups to show a placebo/active treatment difference is 2100 i.e. 1050 patients per group. The following 6 assumptions have been made:

1. Mean follow-up 5 years (range 3 to 6 years but greatest recruitment at start).
2. Non-fatal plus fatal stroke events = 40/1000 patient years.
3. Total non-stroke mortality = 70/1000 patient years.
4. Overall Type I error = 1%.
5. Power = 90%.
6. Stroke events exclude transient ischaemic episodes and amaurosis fugax.

In view of the high non-stroke mortality only 1400 of the 2100 patients are expected to survive 5 years. A recent meta-analysis of all the antihypertensive trials in patients aged >80 years[13] revealed a 10.8% incidence of fatal plus non-fatal strokes over 3.5 years in the placebo groups (approximately 30/1000 patient years). The meta-analysis included mainly patients with ISH and this is expected to underestimate events in the combined systolic and diastolic hypertension HYVET trial.

Stroke events in patients aged >60 years with ISH in the Syst-Eur trial[6] were 13.7/1000 patient years with placebo. However, adjusting for age (mean age 70 years in Syst-Eur, 85 years in HYVET) gives an expected rate of 44/1000 patient years. TIAs have not been included in the calculations as an end-point. The combined systolic and diastolic hypertension EWPHE trial[3] had 40/1000 patient years stroke events. If active treatment reduces stroke events by 35% then 160 strokes would be expected in the placebo group (adjusting for total mortality) and 105 in the actively treated groups. A 36% reduction was observed in the meta-analysis.

Three interim analyses are planned based on the O'Brien Fleming Guidance Rules.[24] The boundaries will be, first analysis $p < 0.0001$, second $p < 0.001$, third $p < 0.004$, and the last significance level to be taken to give an overall p value of 0.01 (namely $p = 0.009$). A possible complication for the HYVET trial is that the meta-analysis of very elderly patients in randomised controlled trials of antihypertensive drugs[13] suggests a possible 14% increase in total mortality. It is difficult to balance increased mortality against decreased morbidity, but the arbitrary decision has been taken to provide stopping guidance from a similar analysis on total mortality, giving an overall value of 0.05 (2-sided). At this 5% level the trial has 65% power to detect a 14% increase in mortality. Asymmetric decision rules will be used to determine an increase in total mortality. Interim analyses will be performed after 70, 140 and 210 stroke events.

In addition, data will be collected in order to examine the trade-off between mortality increase and morbidity decrease (should this be required). The health status will be determined for all patients at the end of the trial. The broad categories will be based on ADL and Disability grading.[25] Statistical analyses will be performed at ICSM, Hammersmith Campus. Both ITT and per-protocol analyses will be undertaken. Patients may have multiple events, but only 1 event of any 1 type will be used in the analyses.

6. Committees

The committee structure is similar to that of the pilot. The members of the committees are detailed at the end of the paper. There is also a National Coordinator for each country who will help with the intricacies of running the trial in their country. The coordinating centre staff will be responsible for the day to day running of the trial.

The Steering Committee will be responsible for agreeing the protocol, any changes to the protocol and for the general running of the trial. The Monitoring and Statistical Committee (Data Monitoring Committee) will be responsible for quality control of the data, monitoring recruitment and other as-

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pects of the trial, and supervising interim analyses (see section 5). The Data Monitoring Committee reports to the Ethics Committee and is supported by staff of the coordinating centre, in particular, the trial coordinator and the statistician. The End-Point Committee will evaluate individual outcomes 'blind' to randomised treatment. Relevant documentation [e.g. ECG, copy of computed tomography (CT) scan report] will be requested for each end-point validated and the source data will be checked for all end-points. Finally the Ethics Committee decides on whether the trial continues or not. They receive the reports from the Monitoring and Statistical Committee and base their decisions on this information and any other evidence that may arise during the course of the trial including results from other studies or trials.

7. Discussion

7.1 Rationale For Change In Design From Pilot Trial

The main trial is a double-blind design that involves the provision of identical placebo tablets. The pilot trial was funded by a charity, the British Heart Foundation, and it was not felt reasonable to ask the organisation to fund the costs of manufacture and distribution of matching placebos. However, the main trial is funded by both the British Heart Foundation and the Institut de Recherches Internationales Servier. This additional funding has made it possible for the manufacture of identical placebos and their distribution throughout the world. However, the provision of active treatment and matching placebo is expensive and also makes the original 3-group design more complicated and costly. It was therefore agreed to have 2 treatment groups, placebo and active treatment, respectively. The design of the pilot study has now been called a PROBE design. This design has been used extensively (STOP I,[4] STOP II,[26] HOT[27]), but has definite disadvantages because the investigator knows the nature of the treatment and the patient knows which treatment they are receiving.

The fact that the investigator knows the nature of the treatment may affect the trial in 4 main ways.

First, when an end-point occurs on no treatment, they may be more likely to ascribe the event to a lack of treatment. For example, a patient who has an MI followed by a stroke may be recorded as having a stroke as the underlying cause of death. If the patient was known to be on active treatment the investigator may decide that the underlying cause was an MI. In a double-blind design the investigator is not certain of the nature of the treatment although he does know the BP level. The element of uncertainty prevents important bias. In the PROBE design a committee evaluates the end-points in a blind fashion but still has to examine the data provided by the non-blinded investigator.

Second, there may well be differential withdrawal of patients from the 2 groups when the investigator is aware of the treatment. At a given level of BP the investigator may be more anxious if the patient is not taking treatment than if they are uncertain as to the nature of the treatment.

Third, in an open trial adverse drug effects will only be diagnosed when active treatment is being given. This means that any untoward events, which are unrelated to drug treatment, will only be recorded in the actively treated groups. Again, double blinding ensures that the adverse events are recorded evenly.

Fourth, there is the problem that the investigator will record BP differently if aware of the randomisation. For example, a patient on active treatment with very high BP may be asked to rest a little longer and a second result recorded. If the patient is known not to be taking treatment then the investigator will not repeat the measurement. A double-blind design removes this source of bias.[28]

There are 2 main consequences that may result from the patient knowing the nature of the treatment. Firstly, there may be differential withdrawal from the 2 groups (as with investigator bias). When the patient is not feeling as well as they should they may withdraw from the trial because they are not on treatment (or because they are on treatment). In a double-blind trial the same events may occur

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but the bias of knowing the treatment is removed. Second, it is very difficult to measure the quality of life of a patient who knows the treatment they are receiving. There is a natural tendency for those receiving drug treatment or placebo to improve[29,30] and this will not occur in those who know they are not receiving active treatment.

There are disadvantages to a double-blind trial, apart from the cost of provision of identical treatments, and it is possible that investigators and patients may be less willing to take part. It is also important for the double-blind trial that the treatment code may be broken in an emergency, for example when an anaesthetist is embarking on an emergency operation. Treatment codes have therefore to be kept in sealed envelopes in a site that is accessible 24 hours a day or the interactive voice system that provides the randomisation details may also be consulted to determine the actual treatment. In the latter event the investigator has to provide the interactive voice system with the details of the patient and why the code has to be broken. With regards to HYVET, another disadvantage with changing the design of the trial is that the patient years accrued in the pilot cannot be used in the main trial. Patients from the pilot can be re-screened and entered in to the main trial if they meet the inclusion criteria.

7.2 Reason For Employing a Low Dose Diuretic and an ACE Inhibitor as Active Treatment

Studies have demonstrated the long term efficacy of diuretics in the prevention of cardiovascular morbidity and mortality, particularly in elderly patients with hypertension.[3-5,8,9] It cannot be assumed that lowering BP with any antihypertensive drug leads to marked benefit,[31] but the evidence for diuretics has led scientific authorities to recommend their use in the first-line treatment of hypertension.[32] The use of a low dose is recommended in order to minimise adverse effects while maintaining adequate antihypertensive control.

The HYVET drug regimen is based on the antihypertensive diuretic indapamide SR 1.5mg whose BP-lowering effects are established. Indapamide SR 1.5mg does not modify serum cholesterol and triglyceride levels even over long term treatment.[33] Studies in patients with diabetes mellitus taking indapamide for up to 2 years have shown no significant changes in glucose metabolism[34,35] nor in serum sodium levels. Indapamide SR 1.5mg also induces a significant reduction in left ventricular (LV) hypertrophy as a result of a reduction mainly of LV wall thickness.[36] As a diuretic it may, however, reduce serum potassium levels and elevate serum uric acid levels.

The SR formulation of indapamide provides 24-hour antihypertensive control at a lower dose (1.5mg) than the immediate release formulation.[37] Thus its efficacy is maintained and tolerability improved.[33] Clinical trials have confirmed the short and long term efficacy of indapamide SR, both as monotherapy and in combination with other antihypertensive drugs such as calcium antagonists or ACE inhibitors.[38,39]

The ACE inhibitor perindopril was chosen as a second-step therapy. The drug has been shown to lower high BP effectively,[40] comparing favourably with captopril and atenolol,[41] and to provide an additive effect when combined with indapamide. Perindopril once daily provides consistent BP control throughout the 24-hour period, documented by a trough to peak ratio of 75 to 100%.[42,43] Moreover, long term experience with perindopril confirms that it is well tolerated in the elderly.[44,45] It is associated with only a low incidence of first dose hypotension in patients with CHF[18,19] but, like all ACE inhibitors, may cause cough in a number of patients.

The hypotensive effects of perindopril and indapamide are additive, and the combination of an ACE inhibitor with a diuretic has been shown to be well tolerated in various patient groups.

7.3 Justification for Entry and Goal Blood Pressures

The entry criteria for the HYVET main trial are a sitting SBP of 160 to 199mm Hg and a DBP of 90 to 109mm Hg. These are similar to those of the

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pilot study although in that trial entry SBP was 160 to 219mm Hg. At younger ages it is well recognised that an SBP, alone or associated with a high DBP, should be treated if over 160mm Hg. It was felt that this was a suitable pressure to be examined in the HYVET trial. In the pilot study few patients were entered with an SBP over 200mm Hg and therefore these patients are excluded from the main trial as probably needing treatment. However, some patients with a sitting SBP over 200mm Hg may not have a standing SBP over 140mm Hg and the dilemma of treating them will remain. Similar arguments can be put forward for treating diastolic pressures of 90 to 109mm Hg. Many patients aged ≥80 years have a high SBP and low DBP (isolated systolic hypertension) and these are excluded from the HYVET trial. The main reason for excluding them is that the results of the trial must be conclusive and the best probability of success with active treatment is in those with hypertension as found in younger patients. If we show that sustained, systolic and diastolic hypertension will benefit from active antihypertensive therapy then the problem of ISH may be addressed. If HYVET shows a benefit we shall still not know whether SBP of 140 to 159mm Hg should be treated, although there is much speculation in some of the guidelines.[14,32,46] If patients with ISH were to be included in the trial more patients would have to be recruited and more importantly, a negative result would still not rule out the necessity for treatment in the very elderly with combined systolic and diastolic hypertension.

The goal BP of the HYVET trial is a sitting SBP <150mm Hg and DBP <80mm Hg. The goal SBP is lower than as that prescribed in the SHEP trial[5] but the same as for the Syst-Eur trial.[6] It is possible that a lower SBP could be chosen with advantage but with the use of only 2 antihypertensive agents it is unlikely that many would achieve a lower goal SBP. The low goal DBP of 80mm Hg is more contentious as there is still some support for the J-shaped curve in which mortality from coronary heart disease may increase at DBP <85 to 88mm Hg, although possibly only in those with prior cardiac disease.[47,48] This is an epidemiological observation which has not been conclusively observed in randomised clinical trials of treating hypertension, but which has been addressed in an analysis of SHEP participants.[49] The coronary arteries are perfused in diastole and it is possible that a very low DBP may be responsible for coronary deaths at very low diastolic pressures. However, in the active treatment group of the SHEP trial, mean sitting DBP was lowered from 77mm Hg to 68mm Hg and in the Syst-Eur trial from 86mm Hg to 79mm Hg. In both trials active treatment reduced cardiac events. In our view this means it is safe to reduce DBP below 80mm Hg. Furthermore, in the HOT trial[27] the reduction of DBP to <80mm Hg (more strictly the intention to do so) was no more dangerous than the intention to reduce DBP to <90mm Hg or <85mm Hg in patients aged between 50 and 80 years. In the SHEP analysis Somes et al.[49] looked at the BP of those in the treated group who sustained a cardiovascular event compared with those who did not. The DBP of those who sustained an event was 66mm Hg compared with 68mm Hg in those who did not. They suggested that some may be overtreated but also stated 'it is reassuring that patients receiving treatment for ISH never perform worse than patients receiving placebo in terms of CVD events'. The design of the HYVET main trial is such that diastolic levels of 66mm Hg will rarely be achieved and provides another reason for including patients with both systolic and diastolic hypertension as the starting point for investigating the treatment of hypertension in the very old.

7.4 Patients Previously Treated with Antihypertensive Therapy

The protocol for the main trial allows for the recruitment of patients previously treated with antihypertensive agents. This was also the case in the pilot trial. Patients are required to stop any antihypertensive medication prior to the placebo run-in phase. Although there is a general agreement in published guidelines about the lack of evidence for the benefit of treatment for those aged ≥80 years, the decision as to whether to continue treatment in

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those who reach the age of 80 is more contentious. The recently published guidelines of the British Hypertension Society[46] recommend the continuation of treatment.

Firstly, it seems inherently appropriate to differentiate between individuals who have been treated for their hypertension from the age of 65 years and patients who were only diagnosed when they were 78 years of age. Secondly, one would need to consider the presence or not of other risk factors such as diabetes mellitus or LV hypertrophy. Thirdly, one would need to consider if an individual's BP is controlled with single or multiple drugs. If a patient has been treated for many years, has evidence of end-organ damage and requires several drugs to control their BP it would be inappropriate to stop their treatment. If an investigator were to do this, it is highly likely that their BP on placebo would be outside the entry criteria stipulated for the trial. However, if a patient has only started treatment when aged in their late 70s, is only on single drug therapy and has no evidence of end-organ damage, we feel that it is reasonable to stop their treatment and screen them for possible entry. Built into the design of the trial are safety levels, such that should a patient's BP be too high in the placebo run-in period they would not be eligible. Similarly, they would be withdrawn after randomisation if high levels were achieved.

8. Conclusions

The design of the main trial has been described. The main HYVET trial is a double-blind, placebo-controlled trial designed to detect a 35% difference in stroke events between placebo and active treatment in patients with hypertension who are aged ≥80 years. Patients will be eligible for the trial if they have a sustained systolic and diastolic hypertension. 2100 patients will be required, giving a power of 90%, 1% significance level, with the duration of follow-up being 5 years. The 2 treatment groups to be employed are a placebo group and 1 based on a diuretic (indapamide SR 1.5mg daily) with or without an ACE inhibitor (perindopril 2 to 4mg daily). The ACE inhibitor will be added to the diuretic if necessary to achieve a goal DBP of <80mm Hg and an SBP <150mm Hg. HYVET should help to establish the benefit to risk ratio of treating the very elderly patient with hypertension.

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