Exploring the challenges of recruiting to a randomised trial assessing the feasibility of treating White Coat Hypertension in older people in UK General Practices: A mixed-methods study

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Abstract

Introduction

There is a recognised association between white coat hypertension (WCH) and adverse cardiovascular outcomes in older adults. However, there is no consensus on the management of WCH in this group. The objective of the Hypertension in the Very Elderly Trial (HYVET-2) study was to assess the feasibility of randomising 100 patients >75 years with WCH from General Practice in the UK to treatment or usual care. The study did not randomise any patients. In this follow up study, we sought to explore the reasons for not recruiting.

Methods

Using a mixed-methods study design, staff from 29 General Practice (GP) sites and the Clinical Research Network (CRN) in Kent, Surrey, and Sussex (KSS) were sent an online questionnaire about local research facilities and infrastructure, and HYVET-2 study methodology and target population demographics.

Results

Nineteen (19) individuals responded the questionnaires (15 primary care staff, 4 CRN staff). Using a framework approach, we identified six themes summarising challenges to HYVET-2 recruitment. These themes were: established approaches of primary care towards managing WCH in older people, target patient demographics, study design complexity, patient-facing study documents, limited research resources in primary care and identification of eligible patients using existing coding.

Conclusion

Our experience showed that recruiting older people to a WCH study from primary care was not feasible. A national scoping survey amongst primary care physicians in the UK, and a robust patient and public involvement (PPI) targeting older people with WCH might improve recruitment in future studies of WCH in older people.

Background

Hypertension remains a major risk factor for morbidity and mortality associated with cardiovascular diseases. Guidelines for the management of hypertension have recommended treatment, to reduce cardiovascular risk, irrespective of the patient's age. The Hypertension in the Very Elderly Trial (HYVET) and Systolic hypertension in Europe (SYST-EUR) studies showed anti-hypertensive therapy in patients between 60 and 80 years old, respectively, to be beneficial especially with a BP target of < 120mmHg. The HYVET study was a randomised controlled trial assessing the benefits of treating hypertension in patients 80 years and older. HYVET showed significant reduction in rate of strokes, deaths from strokes, deaths from any cause, death from cardiovascular causes and heart failure. Further sub-group analysis of the HYVET study showed that nearly 50% of the study participants were noted to have white coat hypertension.

WCH, a phenotype of hypertension, is defined as elevated clinic blood pressure (BP) with normal home or out of clinic BP. Thirty-five percent (35%) of patients who have elevated clinic BP have WCH and this is more common in older people. A recent meta-analysis shows untreated WCH to be associated with increased risk of cardiovascular events and mortality, further raising awareness about the need for its management. However, there are no established treatment guidelines in the UK for WCH beyond recommendations for blood pressure monitoring and follow up. Across Europe, UK and USA, current guidelines do not recommend pharmacological treatment for WCH apart from lifestyle modifications. The USA and Europe make further recommendations for annual follow up.

HYVET-2 was a multi-centre, open-label study assessing the feasibility of conducting a randomised controlled trial to treat white coat hypertension (WCH) in the very elderly (> 75 years of age). It was planned to randomise participants 1:1 to a treatment arm with antihypertensive drugs (Indapamide MR and Perindopril Erbumine) or control arm (no treatment). It was anticipated that this design would provide preliminary data to inform a definitive future randomised controlled trial (RCT).

The HYVET-2 study was planned to recruit from GP practices in the United Kingdom, supported by the Kent, Surrey and Sussex (KSS) Primary Care Clinical Research Network (CRN), which is a National Institute for Health Research (NIHR) regulated agency for research delivery and protection and involvement of patients and the public in research. Prior to the start of HYVET-2, an initial feasibility assessment highlighted potential challenges for recruitment, and feedback was obtained from local research team members at various primary care practices leading to amendments to the study protocol. Over a period of 17 months, 29 sites were activated and 104 potentially eligible HYVET 2 participants were identified. Ten patients consented to be randomised; however, no patients were eventually randomised, as none of them fulfilled inclusion criteria. As the study progressed the trial manager gathered verbal feedback on recruitment challenges. Sites were requested to recruit a minimum of 2 participants each.

In the UK it has been a historical problem to recruit to RCTs, with only 31% of RCTs meeting their recruitment targets and 45% recruiting fewer than 80% of their target. The reasons for this situation are multiple, such as anxiety about study interventions, travel distance to study site, inflexible appointment times and long study assessments. These challenges are more pronounced when it comes to recruitment of older adults. HYVET-2 was novel, as it is the only RCT developed to investigate the feasibility of treating WCH, potential benefits and/or adverse effects. It was felt that a more in-depth evaluation of
the challenges associated with why we did not recruit would be of benefit, not only to the research team, but also to funders of future research investigating WCH, the Clinical Research Network (CRN) and the wider research community in the UK, and internationally.

**Study objective**

To explore the reasons why HYVET-2 did not recruit patients from the perspective of local PIs and research nurses in primary care settings, study team, and CRN supporting staff.

**Methods**

**Study Design**

A mixed-methods study was conducted using a non-validated questionnaire (*Appendix 1*) administered online using Qualtrics. The aim of the twenty-eight (28) questions in the questionnaire was for participants to provide responses/comments that in their opinion contributed to not recruiting to HYVET-2. The questionnaire covered areas relating to GP site-related factors, study methodology, patient-related factors, and staff perceptions about management of white coat hypertension. We gathered details of primary care sites research infrastructure, and previous research experience. For each question, respondents were given the option to tick one box: 'agree', 'disagree', 'neither agree nor disagree', or 'no response'. Respondents to the questionnaire were offered an invitation to participate in a follow up qualitative interview. Of the 19 respondents, 4 accepted to be interviewed but due to challenges of COVID pandemic, interviews did not happen since interested individuals were re-deployed to other clinical roles.

**Recruitment of respondents**

Invitation emails explaining this mixed-methods study were sent to GP site staff and local CRN teams asking them if they would be interested in participating in a questionnaire study. The invitation included a link to an online questionnaire where participants were asked to tick a box at the beginning of the questionnaire "I consent to take part in this questionnaire". A reminder was sent in the subsequent six to eight weeks.

At the end of the questionnaire, respondents were asked if they were happy to be contacted by a member of the research team to participate in a subsequent interview.

A Participant Information Sheet (PIS) and a consent form for a subsequent detailed interview were sent out. The interviews were to be conducted remotely by telephone or Zoom Education, based on participants' preference and time availability.

**Permissions**

The study was conducted in accordance with the standards laid out in the UK Policy Framework for Health and Social Care Research (2017) and the University of Sussex Code of Practice. Ethics approval was obtained on 09-October-2020 (HRA Ref 20/YH/0253). The questionnaire had a consent question at the beginning. If answered 'yes', consent was then implied by the completion of the questionnaire. The study was approved by the funder (Dunhill Medical Trust) and residual funds from the main HYVET-2 grant were used to support this study.

**Results**

Study questionnaires were sent to the 29 GP practices who participated in the HYVET 2 study in the Kent, Surrey, and Sussex (KSS) region of the UK. Respondents were GPs, research nurses and local staff working in the General Practices site and Clinical Research Network (CRN).

Nineteen responses were obtained 8 general practitioners, 7 nurses and 4, details are outlined in Table 1. Figure 1 outlines the years of experience of study respondents.

Six thematic areas were identified as factors for not recruiting to HYVET-2 study. These themes are summarized in Tables 2-6. Upon interviewing study participants about frailty and multi-morbidity of potential study participants, 52.6% and 47.2% of respondents agreed that both frailty level and multi-morbidity respectively were too high to enable study recruitment. (Details in Table 3). Sixty-three percent (63%) of study respondents stated that eligible study population had other co-morbidities and didn't want to participate.

Fifty-eight percent (58%) of study participants agreed that the inclusion criteria were too narrow and 21% agreed that the exclusion criteria were too broad. (See details in Table 4). More than half of respondents (52%) agreed that the recruitment target age of 75 years and above, should have been lower, 10.6% disagreed, 26.2% neither agreed nor disagreed and 10.6% did not provide a response.

Regarding the number of study visits, 42.1% of respondents agreed there were too many study visits for participants and 57.7% agreed study visits were onerous for eligible participants.

Responses from study participants relating to patient facing documents showed that 31.4% agreed that potential participants did not like the term 'very elderly', 42.1% agreed that the study information could have been clearer, and 47.4% agreed that the PIS was too long. (Details in Table 5). Thirty-six percent (36.8%) of respondents thought that the study protocol was too ambitious and too complex for primary care settings, while 42.1% of respondents disagreed. Regarding study site resources, 58% and 79% of respondents disagreed that primary care sites did not have the resources to
undertake the study nor had research nurses to support study respectively. Only 10.6% agreed that resources were not available for the study (details in Table 6 below).

A major thematic area identified from the questionnaire was the identification of eligible patients in primary care settings for the study. Sixty-eight percent (68.4%) of respondents agreed that it was difficult to identify potential participants from primary care clinical databases. Fifteen percent (15.8%) of respondents disagreed with this view, while 10.6% didn't give a response, with 5.2% neither agreed nor disagreed.

**Discussion**

**Summary of findings**

This study showed that recruiting older people to a randomised-controlled study of WCH from primary care was not feasible due to several factors. These factors were: established approaches of primary care teams towards managing WCH in older people, target study patient demographics, study design complexity, patient-facing study documents, limited research resources in primary care which all made identification of eligible patients.

**Established approaches of primary care teams towards managing WCH**

The evidence for treating hypertension in older adults is well established. However, treatment of the WCH phenotype remains controversial due to inadequate evidence in existing literature. Limited evidence for WCH in older people includes two post-hoc sub-group analyses of large trials showing benefits. This contention could have led to established perspectives about WCH among primary care practitioners. Although more than 80% of respondents agreed that WCH was an important clinical issue and treatment was relevant to clinical practice, nearly half (42%) of the respondents had concerns about treating WCH with medications. There is a recognition among primary care physicians of the need for intervention in WCH management compared to the current status quo. Our findings are consistent with a study among 7263 GPs across Europe, which showed that nearly half (52%) of GPs treated WCH only in patients with high CVD risk. In their study, exploring the impact of WCH in primary care in Europe and Canada, the practice of non-treatment of WCH was the same (98%) across both study areas. The approach to management of WCH remains unclear; while recommendations have been made for lifestyle modifications similar to the management of pre-hypertension, a more intensive approach using medications has recently been suggested. Healthcare workers’ perceptions are known factors influencing recruitment of ‘vulnerable’ patients. These include physicians’ personal biases, concerns of additional investigations and medications, and their views about patients’ functional status.

Articles exploring the reasons for poor recruitment in RCTs have not fully explored the positionality and reflexivity of recruiters. These factors are relevant because they emphasize recruiters’ personal knowledge and experiences, which ultimately impact on their attitudes toward the entire research process. The dichotomy between a researcher's interest and a recruiter's view on the phenomena under study including scepticism about a study’s usefulness and misunderstanding the trial’s purpose, has undesirable bearings on the success of an RCT especially in areas which remain contentious such as WCH. Patients’ participation in trials is greatly influenced by their healthcare providers’ views about the study especially when recruitment occurs in primary care as in HYVET-2. This arises from how information would be shared with potential participants, thus raising the need for early exploration, addressing and incorporating care providers’ and recruiters’ beliefs and perceptions in study design and planning.

**Target patient demographics**

Shenoy et al. recommend that the age limit for elderly care trials be moved from the standard 65 years and above, to 75 years due to improving life expectancy worldwide, a view that informed the inclusion criteria of HYVET-2, though the original HYVET focused on those 80 years and over. However, our findings showed that more than half of the respondents (>50%) were of the view that the age limit 75 years and older, should have been lower, allowing for more participants to be recruited. This viewpoint is justified by the notion that older adults in the 65-75-year age group are more likely to be interested in health promotion and disease prevention measures (e.g. medical management of WCH), compared to those older than 75 years. Some of the study sites recommended a lower age as it was less likely that the participants would be taking medications for WCH, but in the very elderly age group many were already on antihypertensives with some sites treating WCH patients in this age group. Bourgeois et al reports that only 12.3% of adults 75 years and older have enrolled in CVD clinical trials compared with 42.5% of those older than 65 years. The approach to management of WCH remains unclear; while recommendations have been made for lifestyle modifications similar to the management of pre-hypertension, a more intensive approach using medications has recently been suggested.

With an older adult study population in research, there are additional challenges such as co-morbidities and frailty. Functional status and demographics of patients are determinants for recruitment and retention in research in primary care. Our study showed that more than 50% of respondents considered the level of frailty and existing co-morbidities among eligible participants to be too high, making potential participants unwilling to participate. This finding is consistent with 46% of older adults with neurologic and cardiovascular diseases refusing participation in trials. Although the HYVET-2 study protocol did not consider frailty status as part of its exclusion criteria, recruiters felt this was important especially with the age group under study. Number of medications already being taken, mobility challenges, reliance on others due to frail status of potential participants were cited as inhibitors to willingness to participate.
**Study design complexity**

The study complexity, with 9 study visits and extra medications were factors considered onerous for participants and their carers by nearly 57% of respondents, although this is the view solely from the research team members and not potential participants. As an interventional trial, the introduction of another medication leading to probable polypharmacy among potential participants is germane. Several patients might not want to take additional medications to those they are taking for their chronic conditions. Study visit challenges could be addressed by providing means of transport, payment of travel tickets and other incentivisation strategies to boost study recruitment\textsuperscript{16,48,49,58–61}. Alternatively, home visits could have been used to reduce the burden of numerous study visits.

**Patient-facing documents**

Nearly half of the respondents (47%) observed that the information for potential participants in the PIS was lengthy and the wording could have been clearer and easier to understand. Communication is critical to successful recruitment in research. This includes, but is not limited to, how consent is sought, the PIS, use of open/closed ended questions and medical jargon in patient-facing documents\textsuperscript{15,62}. For a feasible trial for managing WCH in older people, an early consultation and collaboration with holder patients and their families/ carers would be essential. This would bring to the fore the perceptions, preferences, and treatment options of potential participants for incorporation into the study design.

**Limited resources in primary care for research**

The challenges of recruitment in primary care settings may be more than those encountered in secondary/tertiary health centres especially during COVID times. The success of the original HYVET study\textsuperscript{5} and other blood pressure studies such as SPRINT\textsuperscript{63} could be attributable to study settings which were multi-national, multi-centre and secondary/tertiary-facility based as compared to the three-county, multi-centre, primary care settings of HYVET-2. There is more support and resources available at secondary/tertiary levels of healthcare compared with the resources and demands on staff in primary care.

**Identification of eligible participants**

Recruitment in RCTs across multiple centres is generally slower and more difficult than expected, due to the differences in research infrastructure and human resource across different sites\textsuperscript{33}. The challenge becomes pronounced in complex trials which require additional resources. Although respondents disagreed that the study was overly complex and ambitious for their primary care settings, identifying potential participants with WCH from their clinical databases, was found to be difficult at nearly 70% of study sites. Central to recruitment is the ability to identify potential participants. Different clinical database systems and application software are used across primary care settings in the UK. This lack of uniformity makes identification of potential participants difficult especially if there are no clinical codes for WCH in software applications. This situation could lead to a decline in physician commitment since recording a diagnosis and ultimately identification of potential participants becomes difficult\textsuperscript{57,64}. Data quality within electronic records of a practice was also highlighted as an issue. Different GPs in the same practice might record data differently. Again, it was assumed that ABPM data (searching electronic ABPM records) would be the primary source of participant identification. However, most sites did not store ABPM data in a searchable way. Although differences in practice settings were contributory factors for recruitment success, the crux remains whether primary care practitioners are diagnosing WCH in their practice irrespective of the application software systems used. Humbert et al. reports that across Europe, 49.3% of GPs diagnosed WCH and 52.1% were unaware of any guidelines for WCH\textsuperscript{26}.

**Study Limitations**

An interview between study participants and members of the research team would have provided a more in-depth data than what was captured in online questionnaire. However, the emergence of the COVID-19 pandemic disrupted the data-collection process and the four staff who initially expressed interest in being interviewed later declined due to redeployment and additional work commitments.

**Recommendations for future research and policy**

Due to challenges peculiar to older adults such as multi-morbidity, frailty, reduced mobility, polypharmacy among others\textsuperscript{20,21}, RCTs in older age groups need careful planning, interaction with PPI, incorporating potential participants’ views, with significant attention given to research infrastructure at various multi-centre settings. It is recommended that future WCH research should adopt fewer hospital study visits.

Future research into WCH must first identify, through a scoping survey, geographical areas in the UK and worldwide with known prevalence of WCH for delivering feasible RCTs. An existing database of WCH patients should be available to make identification of potential participants easier.

With regards to policy, applications used across various primary care facilities should have specific coding for WCH. This approach should be coupled with clarity in guidelines concerning WCH diagnosis. There is a need to identify whether clinicians are diagnosing WCH in their practice and how they manage it. This knowledge would inform standardisation of practice, new guidelines, and future research. Furthermore, older patients with more co-morbidities and frailty should be supported to participate in research.

**Declarations**

All methods used in the study were carried out in accordance with relevant guidelines and regulations or declaration of Helsinki.

**Data availability**
The datasets generated and/or analysed during the study is available on request from the corresponding authors.

**Conflict of Interests**

All authors (EM, KA, MO, SB, CM, NP, CR) declare they have no competing conflict of interests. Researchers KA, MO, SB, NP, CR are part of the original HYVET-2 study and CR was part of the very first HYVET study.

**Author contributions**

All authors contributed to the writing of the study protocol. EM, KA, MO, SB, CM, NP, CR wrote this paper. SB was the study statistician and offered statistical input in the analysis. All authors reviewed the final manuscript.

**Ethical approval and consent to participants**

The study has full ethical approval by the NHS Health Research Authority with REC reference number (HRA Ref 20/YH/0253) given on 09/10/2020. It is being sponsored by the University of Sussex. The ISRCTN registration number is 13127656 (on 12/07/2018) and EudraCT registration number is 2017-004004-22. Written informed consent was obtained from all study participants and/or their legal guardian(s) for taking part in the study and publication of its findings.

**Consent to publication**

Not applicable.

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* **Trial Steering Committee:** Francesco Cappuccio (Chair), Ruth Peters, Rosemarie Hutchinson, Richard Quirk, Chakravarthi Rajkumar (Chief Investigator), Khalid Ali (Co-investigator), Mike Okorie (Co-investigator), Stephen Bremner (Statistician), Colin McAlister (CTU Trial Manager), Nicky Perry (Clinical Trials Unit Director)

* **Data Safety Monitoring Committee:** Chris Kingswood, Nicola Gainsborough, Winston Banya.

* **Investigators at primary care sites:** T. Sevenoaks (Brockwood), H. Wilson (Mid Sussex), V. Short (Newton Place), J. Thompson (Cossington House), P. Deffley (Trinity Medical Centre), P. Vinson (Furnace Green), O. Snape (Henfield), R. Danson (Woodbridge Hill), S. Fairhead (Cleveleys Group), R. Thakur (Pendle View), O. Mariscal (Eric Moore Partnership), A. Ajala (Colte Partnership), S. Davies (West Walk), R. Reed (Mendip Vale), H. Davies (The Lennard), G. Sanderson (Stockwell Road), R. Horsley (The Ridings), H. Nobeebaccus (Gilberdyke), E. Dobson (Diadem), S. Sukumar (High Street), N. Thobile (Bartholomew), N. Fielden (Hillfoot), G. Khan (Newton Surgery), C. Johnston (Church Street), N. Thomas (Windrush).

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11. This resource is a joint production of the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) Greater Manchester and the British Hypertension Society.


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Tables

Tables 1 to 6 are available in the Supplementary Files section

Figures
Figure 1

Bar chart showing years of experience of respondents

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TABLESHYVET2study.docx