Institution: The University of Brighton		
Unit of Assessment: A3 – Allied Health Professions, Dentistry, Nursing and Pharmacy		
Title of case study: Defining targets for effective hypertension management in the very elderly		
Period when the underpinning research was undertaken: 2007 – 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Chakravarthi Rajkumar	Professor and Chair in Geriatric and Stroke Medicine	2005 – to date
Period when the claimed impact occurred: 2013 – 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Brighton and Sussex Medical School (BSMS) research into hypertension has, for the first time, provided blood pressure targets for the very elderly (> 80 years) to reduce the risk of death due to stroke or heart attack. Prior to this, there was no defined targets for blood pressure in this age group. The effective target of 150/80 mmHg, identified in the research, underpin recommendations in NICE guidance (UK) on cardiovascular diseases and blood pressure management, as well as international healthcare guidelines in Europe, USA, Canada and China. This has resulted in improved clinical practice in England with 86.5% of patients with arterial disease now meeting the revised target blood pressure of 150/80 mmHg, leading to improved health outcomes.

2. Underpinning research

An estimated 1,130,000,000 people worldwide have hypertension with the condition affecting approximately one third of adults in the UK; however, this figure rises to more than two in three for those over the age of seventy-five. Hypertension causes brain clots and blocked arteries, which can result in strokes or heart attacks. Although a number of clinical trials have shown the benefit of hypertensive drug treatment on stroke, cardiovascular events and mortality, very few studies include the very elderly (corresponding to WHO 'oldest-old' as people aged 80 years and over) or have recruited too few to show an advantage of treatment. This has not only generated concerns that treatment for this demographic may be harmful, but it also raises ethical questions over whether this population is being denied the opportunity to benefit from clinical treatment.

In 2000, the HYVET Trial was conceived to provide the research evidence required and to resolve persistent areas of clinical uncertainty about the relative benefits and risks of antihypertensive treatment in this neglected patient group. The trial built on early collaborative research findings from trials of hypertension treatment to which Professor Chakravarthi Rajkumar was a co-investigator. The HYVET Trial (2000 – 2008) was funded by the British Heart Foundation and the pharmaceutical company, the Institut de Recherches Internationales Servier. It was led by Professor Bulpitt (Hammersmith Hospital, Imperial College) and Professor Fletcher (London School of Hygiene and Tropical Medicine) with Rajkumar contributing expertise through the role of national coordinator for the UK, and analysis of the results for the full duration of the project [reference 3.1]. Rajkumar was a Senior Registrar and Senior Lecturer at the Hammersmith Hospital before joining the University of Sussex in 2005 where he led the project to its completion in 2008.

The HYVET trial enrolled 3,845 patients aged 80 years and over, at 195 centres in 13 countries across Western and Eastern Europe, as well as in China, Australasia and North Africa. The participants enrolled had a sustained systolic blood pressure of 160 mmHg at entry into the trial. The therapeutic intervention was 1.5mg of the diuretic drug *indapamide* against matching placebo. The angiotensin-converting enzyme (ACE) inhibitor *perindopril* was added in a dose of 2 or 4 mg if necessary, in order to achieve a target blood pressure of 150/80 mmHg [3.1].

Increasing age is a major predictor of death from stroke, with rates as high as 52% in persons 80 years of age or older. After 2 years of treatment the mean blood pressure reduced by 15/6.1 mmHg in the active treatment cohort. This group also showed a 30% reduction in the rate of fatal or non-fatal stroke, a 39% reduction in the rate of death from stroke, a 21% reduction in the rate of death from any cause, a 23% reduction in the rate of death from cardiovascular causes, and a 64% reduction in the rate of heart failure. The trial also showed that there were significantly fewer serious adverse events in the active treatment group, with the baseline characteristics of the two patient groups well matched in terms of previous cardiovascular events and diabetes [3.1].

A parallel study into ambulatory blood pressure (ABP) monitoring was led by Rajkumar as part of the main trial [3.2]. ABP was measured in 284 participants recruited to the HYVET trial. This analysis showed that 50% of the main trial participants satisfied the criteria for White Coat Hypertension based on daytime ABP monitoring. White Coat Hypertension is a phenomenon in which patients exhibit a higher blood pressure level in a clinical setting than in other contexts such as their home. The findings of this parallel study, paired with the results of the main trial, suggest that treating White Coat Hypertension in the over 80s might confer some protection to future cardiovascular events. In the same ABP monitoring sub-study, Rajkumar and colleagues also showed that reduced arterial stiffness at night might partly explain the marked benefits observed in the main trial [3.3].

The HYVET trial, and parallel studies, provided the first conclusive evidence that blood pressure-lowering drug treatments significantly benefit people aged 80 years or older. It also provided an indication of the blood pressure threshold to target for effective management of hypertension in the very elderly.

3. References to the research

[3.1] Beckett, N. S., Peters, R., Fletcher, A. E., Staessen, J. A., Liu, L., Dumitrascu, D., Stoyanovsky, V., Antikainen, R. L., Nikitin, Y., Anderson, C., Belhani, A., Forette, F., Rajkumar, C., Thijs, L., Banya, W., & Bulpitt, C. J. (2008). Treatment of Hypertension in Patients 80 Years of Age or Older. *New England Journal of Medicine*, *358*(18), 1887–1898. https://doi.org/10.1056/NEJMoa0801369 [Quality validation: HYVET was voted unanimously as the 2008 Trial of the Year by the prestigious Project ImpACT (Important Achievements of Clinical Trials) and the Society for Clinical Trials and judged to have provided the basis for a substantial, beneficial change in health care and to be a landmark clinical trial in terms of design, execution, and results. https://www.sctweb.org/toty.cfm

[3.2] Bulpitt C. J., Beckett, N., Peters, R., Staessen, J. A., Wang, J., Comsa, M., Fagard R. H., Dumitrascu, D., Gergova, V., Antikainen, R. L., Cheek, E., and Rajkumar, C., (2013). Does White Coat Hypertension Require Treatment Over Age 80? *Hypertension*, *61*(1), 89 – 94. https://doi.org/10.1161/HYPERTENSIONAHA.112.191791 [Quality validation: published in leading peer-reviewed journal].

[3.3] Bulpitt, C. J., Webb, R., Beckett, N., Peters, R., Cheek, E., Anderson, C., Antikainen, R., Staessen, J. A., and Rajkumar, C. (2017). Antihypertensive treatment decreases arterial stiffness at night but not during the day. Results from the Hypertension in the Very Elderly Trial. *Blood Pressure*, *26*(2), 109–114. https://doi.org/10.1080/08037051.2016.1219222 [Quality validation: published in leading peer-reviewed journal]

4. Details of the impact

The HYVET Trial provided the research-based evidence needed to establish a blood pressure target within national and international healthcare guidelines. This measure is specifically for the treatment of hypertension in the over 80s. Prior to this study, this patient group had been neglected with no appropriate measure available to guide clinical practice in relation to these patients. As a result General Practitioners in England now have a set blood pressure threshold to refer to when considering hypertensive treatment in this age group.

4.1 Providing clinical guidance on hypertension in the UK (NICE) and internationally (USA, Canada, Europe and China)

Research within the HYVET programme provided guidance to physicians and policy-makers to improve standards, assist in the knowledge and training of health care professionals and to help patients make informed decisions about their care. These national guidelines undergo regular reviews to ensure that recommendations provided are based on the most recent and robust research findings.

In the UK, the findings of the HYVET trial were incorporated originally into NICE guidelines as recommendations for the treatment of hypertension in 2011. Following a review of these guidelines in 2019, it was confirmed that these findings remain the critical reference point for guideline committees to base their recommendation for the treatment of hypertension in the very elderly [source 5.1]. Professor Terry McCormack, member of the NICE 2011 Guideline Development Group and the NICE 2019 Guideline Committee on Hypertension confirmed that this study was '*pivotal in setting the standard for the treatment of hypertension in the very elderly*'. Professor McCormack further clarifies that:

'In both instances when considering the optimum blood pressure in the very elderly, the HYVET study provided the most robust and highest quality evidence compared to all the other studies reviewed. Based on the trial results, the 2011 Guideline Development Group recommended that people aged 80 years old and over […] should be treated to a clinic blood pressure target of under 150/90mmHg, as defined by the HYVET Trial. This recommendation was sustained in the updated version of the guideline published in August 2019 […] Based on their experience the [NICE 2019] committee members agreed to retain the recommendation from the 2011 guideline, which was based on the HYVET Trial - the only large, outcome-based randomised controlled trial in this age group' [5.2, 5.3].

HYVET is the key evidence cited in international guidelines to treat high blood pressure in people aged 80 years and over [5.4], and by providing this guidance to healthcare professionals worldwide, the HYVET study has contributed to '*an improved quality of care*' [5.2]. The international guidelines that utilise the HYVET results to evidence their recommendations include the American College of Cardiology and American Heart Association guidelines, the Hypertension Canada Guidelines, the European Society of Cardiology/European Society of Hypertension guidelines, and the Chinese guideline for the management of hypertension in the elderly. Each set of guidelines adopts a rigorous, evidence-based approach to recommend treatment thresholds, goals and medications in the management of hypertension in adults and grade the quality of evidence. Recommendations are made based on their effect on prioritised outcomes. Adopting this stringent evidence-driven process, the authors of these guidelines, drawn from a significant pool of international experts in the field, cited the HYVET Trial as one of the critical studies for clinical effectiveness of the treatment of hypertension in the very elderly.

One of the most influential guideline updates is the eighth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC8) published by the American Medical Association in 2014 that replaces the previous guidelines published in 2003. Panel members appointed to this review developed evidence statements and recommendations for blood pressure treatment based on a systematic review of the literature to meet user needs and the needs of the primary care clinician.

Randomised controlled trials, including the HYVET study, formed the basis of these new guidelines, as they represent the gold standard for determining efficacy and effectiveness. In this guideline the recommendation to initiate pharmacologic treatment to lower BP to 150/90 to treat patients over the age of 60 (including the very elderly) was given a Grade A recommendation, the strongest grade given to recommendations where '*there is high certainty based on evidence that the net benefit is substantial*' [5.5].

4.2 Changing clinical practice and the treatment of hypertension in the very elderly in England

Due to the introduction of a new blood pressure target for the very elderly, based on the HYVET findings, monitoring of clinical practice data is now available. In March 2015 a review of the adoption and implementation of NICE Guidance CG127 (2011), showed that 85.6% of patients in England with peripheral arterial disease had their last blood pressure reading (measured in the preceding 12 months) set at 150/90mmHg or less [5.6]. This is directly in line with NICE Guidance for Recommendation 1.5.6 based on the HYVET Trial. NICE generate Quality Standard (QS) for GPs and other care providers to use to evaluate their current practice and understand how to improve care. The uptake of the NICE QS is measured via various national records such as the Quality Outcome Framework (QOF). QOF is a voluntary annual reward and incentive programme for all GP practices in England. It consists of a set of achievement measures, based on the NICE indicators, against which GP practices are scored and rewarded financially. The QS28 'Hypertension in Adults' Statement 4 is based on the HYVET Trial findings that recommends '*people with treated hypertension have a clinic blood pressure target set to below 140/90 mmHg if aged under 80 years, or below 150/90 mmHg if aged 80 years and over*.' As part of its uptake assessment, QOF recorded the percentage of patients with hypertension in whom the last blood pressure reading (measured in the preceding 12 months) was 150/90 mmHg or less. Data collected from GP practices across England, in March 2016, March 2017 and March 2019 showed that 79.6%, 80% and 79.7% of patients reached this blood pressure target, respectively [5.7]. These data confirm that the blood pressure targets in the very elderly, informed by the HYVET trial, have been met in up to 80% of patients treated for hypertension at GP practices in England.

5. Sources to corroborate the impact

[5.1] NICE Guideline on Hypertension in adults: diagnosis and management. Clinical Guideline [NG136] Appendix D. Evidence review for targets, March 2019 https://www.nice.org.uk/guidance/ng136/documents/evidence-review-4 [Accessed 16 March 2021; PDF available].

[5.2] Testimonial from Prof Terry McCormack Vice-President of the British and Irish Hypertension Society and Member of the NICE Hypertension in Adults Guideline Committee and 2011 and 219. This testimonial corroborates the claim that the HYVET Trial was the only robust research-based evidence available at the time when the NICE Committee revised the NICE Hypertension in Adults Guidelines 2011 in 2019.

[5.3] NICE Guideline on Hypertension in adults: diagnosis and management. Clinical guideline [NG136]. Last updated: August 2019 https://www.nice.org.uk/guidance/ng136/resources/hypertension-in-adults-diagnosis-and-management-pdf-66141722710213 [PDF available].

[5.4] Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. JACC. 2019:71(19) e127-248. [PDF available].

Williams, B., Mancia, G., Spiering, W. et al, 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018; 39:3021–3104 [Accessed 16 March 2021].

Hypertension Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children. Canadian Journal of Cardiology, 2018, volume 34, Issue 5, 506-525 [PDF available].

2019 Chinese guideline for the management of hypertension in the elderly. J Geriatr Cardiol 2019; 16: 67□99. doi:10.11909/j.issn. 1671-5411.2019.02.001 [PDF available].

[5.5] 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507-520. doi:10.1001/jama.2013.284427 [PDF available].

[5.6] Uptake data of the NICE Guidance on Hypertension in Adult, NCG127 recommendation 1.5.6, data provided for March 2015. Source Health and Social Care Information Centre. Quality Outcomes Framework. [Webpage archived; PDF available].

[5.7] Uptake data of the NICE Quality Standard QS28 statement 4 related to the NICE Guidance on Hypertension in Adults (NG136, 2019), data provided for March 2016, March 2017 and March 2019. Source Health and Social Care Information Centre. Quality and Outcomes Framework. [Webpage archived; PDF available].