Institution: Imperial College London

Unit of Assessment: 02 Public Health, Health Services and Primary Care

Title of case study: Global Change in Guidelines Relating to Treatment of the Very Elderly Resulting from HYVET (Hypertension in the Very Elderly Trial)

1. Summary of the impact (indicative maximum 100 words)

Before the Hypertension in the Very Elderly Trial (HYVET) it was not clear whether people aged 80 and over with hypertension should receive antihypertensive treatment. The over 80s are one of the fastest growing groups in society and are at high risk of hypertension and its sequelae due to age. HYVET demonstrated benefit of treatment including reduced mortality and cardiovascular comorbidity. Guidelines around the world for the treatment of hypertension have changed as a result. In the UK it is proposed that the Quality Outcomes Framework (QOF) for GPs now includes those over 80 and uses the target blood pressure used in HYVET.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor Christopher Bulpitt, Professor of Geriatric Medicine (1989-2005), now Emeritus Professor and Chief Investigator of HYVET
Dr Nigel Beckett, Clinical Research Fellow, Honorary Consultant Physician and trial coordinator (1998-2010)
Dr Ruth Peters, Senior Researcher and deputy trial coordinator (1997-present)

HYVET is the only multinational double blind randomised placebo controlled trial of antihypertensives in those aged 80 and over. HYVET was sponsored, directed, coordinated and managed by an Imperial team led by Professor Bulpitt. Prior to HYVET the balance of risks and benefits from antihypertensive treatment in this very elderly group were not clear and guidelines were equivocal. A multinational open label pilot trial from the same Imperial-led group (1) preceded the main HYVET trial allowing piloting of methodology.

Professor Bulpitt and Imperial colleagues were responsible for securing and managing the funding, design, data collection, processing, statistics, pharmacovigilance, endpoint identification and, validation, quality assurance, monitoring and day to day running of the trial in all countries/centres.

3845 Hypertensive participants (systolic blood pressure ≥160mmHg at trial entry) aged 80 or over at time of randomisation were recruited from 195 centres in Eastern and Western Europe, China, Australasia and Tunisia and randomised to antihypertensives, a thiazide like diuretic (Indapamide sustained release 1.5mg) +/-an angiotensin converting enzyme inhibitor (perindopril 2-4mg) or matching placebos. Participants were seen every 3 months in the first year then 6 monthly thereafter. Mean follow up was 2.1 years when the trial was terminated early at the time of the second interim analysis due to a significant reduction in total mortality in the actively treated group.

Key results from the main trial indicated that antihypertensive use was associated with a 21% reduction in total mortality, a 37% reduction in stroke, a 34% reduction in cardiovascular events, a 64% reduction in incident/worsening heart failure, a 42% deceased risk of fracture and no negative impact on cognitive decline/dementia (2-4).

A one year open label extension followed, carried out by the same team. It found that very elderly patients with hypertension may gain early benefit from treatment in terms of stroke and cardiovascular events but that treatment for more than 12 months may be needed to achieve reductions of cardiovascular and total mortality. The results reinforce the benefits from treatment and support the need for both early and long term treatment (5).

Substudies included Ambulatory Blood Pressure Monitoring (ABPM; showing a high prevalence of

white coat hypertension and a potential gain from treatment in this group) and Quality of Life (showing no detriment associated with antihypertensive treatment) (6).

3. References to the research (indicative maximum of six references)

(1) Bulpitt, C., Beckett, N., Cooke, J., Dumitrascu, D., Gil-Extremera, B., Nachev, C., Nunes, M., Peters, R., Staessen, J., Thijs, L., on behalf of the HYVET–pilot investigators. (2003). Results of the pilot study for the Hypertension in the Very Elderly Trial. *Journal of Hypertension*, 21 (12), 2409-2417. DOI. Times cited: 140 (as of 4th November 2013 from ISI Web of Science). Journal Impact Factor: 3.80

(2) Beckett, N., Peters, R., Fletcher, A.E., Staessen, J., Liu, L.S., Dumitrascu, D., Stoyanovsky, V., Antikainen, R., Nikitin, Y., Anderson, C., Belhani, A., Forette, F., Rajkumar, C., Thijs, L., Banya, W., Bulpitt, C., for the HYVET study group. (2008). Treatment of hypertension in patients 80 years of age or older. *New England Journal of Medicine*, 358 (18), 1887-1898. DOI. Times cited: 652 (as of 4th November 2013 from ISI Web of Science). Journal Impact Factor: 51.65

(3) Peters, R., Beckett, N., Forette, F., Tuomilehto, J., Clarke, R., Ritchie, C., Waldman, A., Walton, I., Poulter, R., Ma, S., Comsa, M., Burch, L., Fletcher, A., Bulpitt, C., for the HYVET investigators. (2008). Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurology*, 7 (8), 683-689. DOI**.** Times cited: 185 (as of 4th November 2013 from ISI Web of Science). Journal Impact Factor: 23.91

(4) Peters, R., Beckett, N., Burch, L., Vernejoul, M., Liu, L., Duggan, J., Swift, C., Gil-Extremera, B., Fletcher, A., Bulpitt, C. (2010). The effect of treatment based on a diuretic (indapamide) {+/-} ACE inhibitor (perindopril) on fractures in the Hypertension in the Very Elderly Trial (HYVET). *Age and Ageing*, 39 (5), 609–616. DOI. Times cited: 9 (as of 4th November 2013 from ISI Web of Science). Journal Impact Factor: 3.81

(5) Beckett, N., Peters, R., Tuomilehto, J., Swift, C., Sever, P., Potter, J., McCormack, T., Forette, F., Gil-Extremera, B., Dumitrascu, D., Staessen, J., Thijs, L., Fletcher, A., Bulpitt, C. (2012). Immediate and late benefits of treating very elderly people with hypertension: results from active treatment extension to Hypertension in the Very Elderly randomised controlled trial. *British Medical Journal,* 344, d7541. DOI**.** Times cited: 12 (as of 4th November 2013 from ISI Web of Science). Journal Impact Factor: 17.21.

(6) Bulpitt, C., Beckett, N., Peters, R., Staessen, J., Wang, J., Comsa, M., Fagard, R., Dumitrascu, D., Gergova, V., Antikainen, R., Cheek, E., Rajkumar, C. (2013). Does white coat hypertension require treatment over age 80? Results of the Hypertension in the Very Elderly Trial ambulatory Blood Pressure side project. *Hypertension*, 61, 89 - 94. DOI. Times cited: 2 **(**as of 4th November 2013 from ISI Web of Science). Journal Impact Factor: 6.87

Awards:

- HYVET was unanimously voted 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 improved the lot of mankind providing the basis for a substantial, beneficial change in health care and to be a landmark clinical trial in terms of design, execution, and results. http://www.sctweb.org/public/about/toty.cfm

Key funding:

- British Heart Foundation (1998-2004; £728,830), Principal Investigator (PI) C. Bulpitt, Hypertension in the very elderly trial.
- Servier International Research (1999-2010; £8,301,643), PI C. Bulpitt, Hypertension in the very elderly trial.
- British Heart Foundation (2000-2005; £143,141), PI C. Rajkumar, Effects of arterial compliance, ambulatory blood pressure, blood pressure variability on morbidity and mortality in hypertension subjects over 80

4. Details of the impact (indicative maximum 750 words)

Impacts include: health and welfare; public policy and services; practitioners and services

Main beneficiaries include: patients; NICE; health professionals; industry; international guideline bodies

The relatively healthy elderly aged 80 and over are one of the fastest growing sectors of the population, both in the UK and globally (in both developed and developing countries). Systolic blood pressure tends to rise with age as does the risk of cardiovascular and cerebrovascular events and dementia. The rise in blood pressure with ageing means that a substantial proportion of those aged 80 and over suffer from hypertension, estimated at ~70% in the UK (Health Survey for England 2009). The results of the HYVET research not only show the reduction in risk of cardiovascular events but the identification of a safe goal blood pressure in this group and are applicable to a large and growing group. This Imperial-led study was the first in this age group and has directly influenced hypertension guidelines internationally.

The results from HYVET have shaped hypertension guidelines in the UK, Europe, Canada, Japan, the USA, China, Russia, Latin America, and South Africa. In the UK the NICE guidelines (2011) indicate that people aged ≥80 should be treated [1] and the consultation on new indicators for the UK 2013/14 Quality and Outcomes Framework (QOF) proposes inclusion of new indicators specifically for the over 80s, using the HYVET goal systolic blood pressure [2].

The European guidelines (2009) now recommend that antihypertensive treatment can be extended to help patients aged 80 years and above, stating that 'gap in the evidence has been filled with...the results of HYVET' [3].

The Canadian Hypertension Education Program (2009) 'specifically recommends that age not be used as a factor in prescribing' based on HYVET results [4]. The Japanese guidelines (2009) now specify that hypertension should be treated in patients of all ages [5; chapter 3] and the adequate antihypertensive treatment is recommended in elderly patients (chapter 8). Guidelines on hypertension in China, Latin America, Russia [6-8] also recommend treatment of high blood pressure in the elderly and cite HYVET. Beyond the ten sources of evidence provided, we can also evidence changes to guidelines in Taiwan and South Africa.

A consensus document in the US on hypertension in the elderly (American College of Cardiology Foundation/American Heart Foundation, 2011) concludes that HYVET provides clear evidence that blood pressure lowering drugs are associated with definite cardiovascular benefits in patients 80 years and over and US guidelines from the National Heart Lung and Blood Institute (JNC8) are expected to include HYVET at their next update [9].

More generally, medical professionals globally have benefitted in terms of receiving clearer guidance, elderly individuals benefit in health terms and health service providers in economic terms. A Swiss group have calculated that applying the results of HYVET means a lower total cost per patient receiving antihypertensive treatment as compared to an untreated group and that the additional medication cost is covered by the reduction of costs related to the treatment of strokes, myocardial infarction and heart failure. The potential decrease in incident dementia and fracture suggests that this may be an underestimate [10].

The pharmaceutical company (Servier) that provided part of the funding and the medication for HYVET report that in the company financial year during which the HYVET results were published their own sales of indapamide (the first line medication used in HYVET) rose by 4% across 11 countries. Data provided by Servier also show generic indapamide sales increasing year on year from 2009 to 2012 with the largest increase in the Sustained Release formulation as used in the trial.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[1] NICE clinical guideline 127 Hypertension: clinical management of primary hypertension http://www.nice.org.uk/guidance/CG127 (pages 136-140). Archived on 4th November 2013. NCGE (Commissioned by NICE) Update of Clinical Guidelines 18 & 24. Hypertension: The

Clinical Management of Hypertension in adults. Clinical Guide 127: Methods, Guides and Clinical Evidence August 2011 (refer to p.171). http://www.nice.org.uk/nicemedia/live/13561/56007/56007.pdf. Archived on 4th November 2013.

[2] National Institute for Health and Clinical Excellence. Consultation on potential new indicators for the 2013/14 Quality and Outcomes Framework (QOF). Archived on 4th November 2013.

[3] Mancia, G., Laurent, S., Agabiti-Rosei, E., Ambrosioni, E., Burnier, M., Caulfield, M., et al. (2009). Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *Journal of Hypertension*, 27, 2121 – 2153 (refer to pp. 2140–2142). DOI.

[4] 2009 Canadian Education Programme Recommendations. The Short Clinical Summary: An Annual Update. 1–17 (refer to p.3). http://www.hypertension.ca/images/stories/dls/09-clinical-summary.pdf. Archived on 4th November 2013.

[5] Ogihara, T., Kikuchi, K., Matsuoka, H., Fujita, T., Higaki, J., Horiuchi, M., Imai, Y., et al, on behalf of The Japanese Society of Hypertension Committee. The Japanese Society of Hypertension: Guidelines for the Management of Hypertension. Chapter 3: Principles of Treatment. *Hypertension Research,* 32 (1): 24 - 28 (refer to p. 26). http://www.nature.com/hr/journal/v32/n1/pdf/hr20083a.pdf. (archived on 4th November 2013) Chapter 8, Hypertension in the elderly. (2009). *Hypertension Research* 32, 57- 62. (refer to p58). http://www.nature.com/hr/journal/v32/n1/pdf/hr20086a.pdf (archived on 4th November 2013)

[6] Liu L. 中国高血压防治指南 2010 2010 Chinese guidelines for the management of hypertension. (2011). *Chinese Journal of Cardiology*, 39(7): 579 - 616. Full copy of the guidelines available on request; refer to p.49 of translated version. http://so.med.wanfangdata.com.cn/ViewHTML/PeriodicalPaper_zhxxgb201107002.aspx. Archived on 26th November 2013.

[7] Ramiro, A., Sanchez, M. A., Baglivo, H., Velazquez, C., Burlando, G., Kohlmann, O., et al on behalf of the Latin America Expert Group. (2009). Latin American guidelines on hypertension. *Journal of Hypertension,* 27, 905-922; refer to p.913.DOI.

[8] Diagnosis & Treatment: Arterial Hypertension. Recommendations of the Russian Medical Society on Arterial Hypertension and the Russian Scientific Society of Cardiology Moscow. (2008); 7 (6), 3 – 32. ДИАГНОСТИКА И ЛЕЧЕНИЕАРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ Приложение 2 к журналу “Кардиоваскулярная терапия и профилактика” (see page 21). Full copy of the guidelines available on request.

[9] Aronow, W., Fleg, J., Pepine, C., Artinian, N., Bakris, G., Brown, A., et al *(*2011). ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly. American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents, American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, European Society of Hypertension. *Journal of the American College of Cardiology,* 57 (20), 2037-2114. (refer to pp. 2074 – 2075). DOI.

[10] Szucs, T., Waeber, B., Tomonaga, Y. (2010). Cost-effectiveness of antihypertensive treatment in patients 80 years of age or older in Switzerland: an analysis of the HYVET study from a Swiss perspective. *Journal of Human Hypertension*, 24, 117-123. DOI.