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NIHR CLAHRC West Midlands News Blog

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NHS National Institute for Health Research

Welcome to the latest issue of your NIHR CLAHRC West Midlands News Blog.

In this issue we have two guest bloggers: Sam Watson who explores the value of ultra-large trials (n>10,000); and Chet Trivedy who discusses the formidable health challenge of the carcinogenic and addictive areca nut. We also look at recent papers on abusive maternal care; fraudulent research; the demographic dividend; and return to our theme of slum health.

We also profile Dr Sarah Flanagan, bring you updates on our PPI, as well as the latest news, events, and our CLAHRC WM Quiz. Finally, we have details of our latest publications.

We hope that you find these posts of interest, and we welcome any comments. You

can find previous issues of our News Blog here.

Original Photo: Paul Rogers

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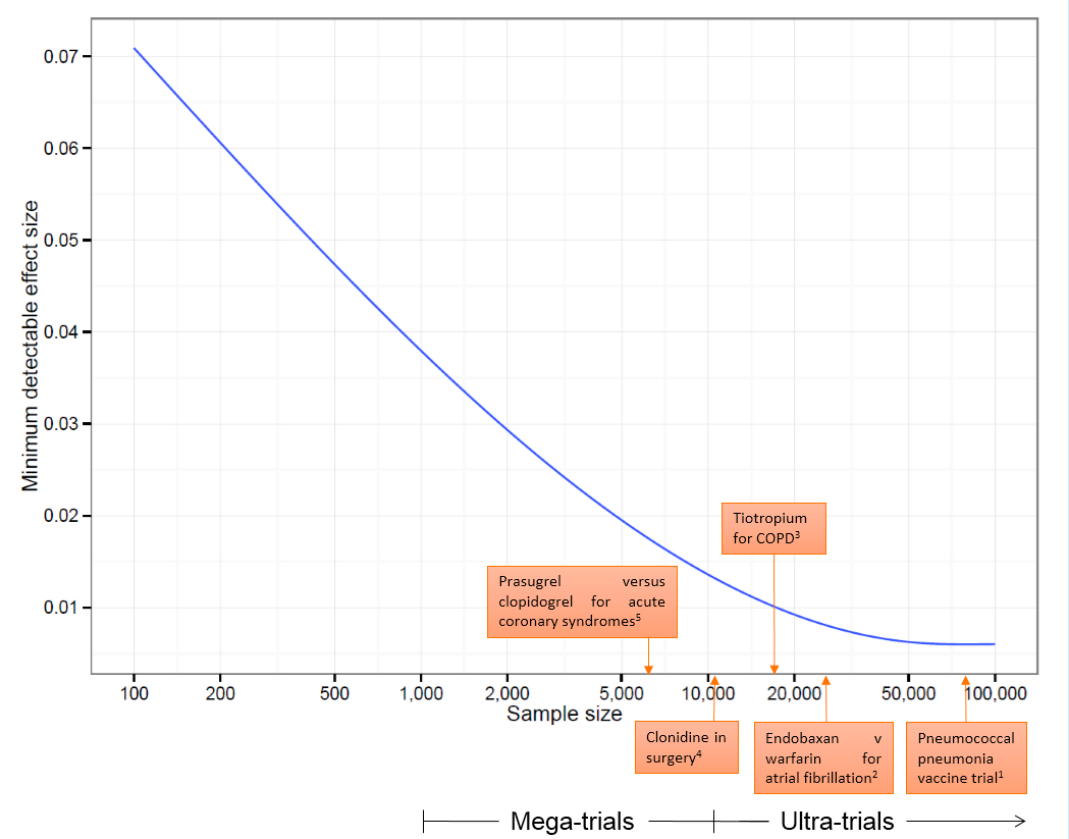
Director & Co-Directors' Blog – Guest Blog

Mega- and Ultra-Trials

Randomised controlled trials (RCTs) are getting larger. Increased sample sizes enable researchers to achieve greater statistical precision and detect increasingly smaller effect sizes against diminishing baseline rates of the primary outcomes of interest. Thus over time, we are seeing an increase in the sample sizes of RCTs, leading to what may be termed mega-trials (>1,000 participants) and even ultra-trials (>10,000 participants). The below figure shows the minimum detectable effect size (in terms of difference from baseline) for a trial versus its sample size (with $\alpha = 0.05$, $\beta = 0.8$ and a control group baseline of 0.1, i.e. 10%), along with a small selection of non-cluster RCTs from the New England Journal of Medicine published in the last three years. What this figure illustrates is that there is diminishing returns, in terms of statistical power, from larger sample sizes.



Nevertheless, with great statistical power comes great responsibility. Assuming that the sample size is large enough that observation of a p-value greater than 0.05 is evidence that no (clinically significant) effect exists may lead to perhaps erroneous conclusions. For example, Fox *et al.* (2014) enrolled 19,102 participants to examine whether ivabradine improved clinical outcomes of patients with stable coronary artery disease.[1] The estimated hazard ratio for death from cardiovascular causes or acute myocardial infarction with the treatment was 1.08 but with a p-value of 0.2, and so it was concluded that ivabradine did not improve outcomes. However, we might see this as evidence that ivabradine *worsens* outcomes. A crude calculation suggests that the minimum detectable hazard ratio in this study was 1.14, and, for a sample of this size, the results suggest that almost 50 more patients died (against a baseline of 6.3%) in the treatment group. One might therefore actually see this as clinically significant.

Similarly, Roe *et al.* (2012) enrolled 7,243 patients to compare prasugrel and clopidogrel for acute coronary syndromes without revascularisation.[2] The hazard ratio for death with prasugrel was 0.91 with a p-value of 0.21. The authors concluded that prasugrel did not “significantly” reduce the risk of death. Yet, with the death rate in the clopidogrel group at 16%, a hazard ratio of 0.91, with a sample size this large, represents approximately 50 fewer deaths in the prasugrel group. Again, some may argue that this is clinically significant. Importantly, a quick calculation reveals that the minimum detectable effect size in this study was 0.89.

Many authors have warned against using p-values to decide on whether an intervention has an effect or not. Mega- and ultra-trials do not reduce the folly of

using p-values in this way and may even exacerbate the problem by providing a false sense of confidence.

-- Samuel Watson, Research Fellow

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CLAHRC International

Areca, the not so healthy nut

The thought of a diet rich in nuts conjures up healthy images, but for the areca nut this could not be further from the truth. *Areca catechu*, often erroneously referred to as the betel nut as it often consumed with the totally unrelated leaf of the betel piper vine (see Figure 1), is a major public health concern across South and East Asia. Data suggests that the areca nut is consumed by a quarter of the world's population and is the third most common substance of abuse after tobacco and alcohol. The habit of chewing areca products is steeped and ingrained so deeply in many of the South and East Asian cultures that it has gained immense popularity in these communities. The habit of areca nut chewing has moved with migratory communities and it is not uncommon to see the tell-tale signs of red spittle (produced as a by-product of chewing areca products) in the streets of London, Birmingham, Leicester and Leeds. Unlike tobacco and alcohol, which are forbidden in some Asian cultures, areca nut is well accepted and even encouraged as an aid to promote digestion after a meal. For children it may be given as a sweet after meals, and as a child growing up in London it was not uncommon to go to the local areca nut (paan) shop on a Friday night after dinner for a round of sweet paan (areca nut with coconut and spices, wrapped up in a betel leaf). The adults would have a different variety of paan, consisting of areca nut mixed with raw tobacco, slaked lime and a mixture of spices. Today this is still a common tradition in many households, even though these practices date back thousands of years to the early Vedic scriptures in ancient India. [1] Further, many religious ceremonies will have the areca nut as its centre and it is often used to mark auspicious events and even as dowry in some cultures. So deep is the cultural and societal acceptance of this humble little nut that the deleterious affects from chewing have been grossly understated.

Figure 1: Areca nuts on betel leaves. *(Image by Ananthy94)*

The areca nut habit has taken a nasty turn since the development of a commercial product known as pan masala. This consists of plastic-packed powdered areca and tobacco and, despite attempts at legislation, is sold on street corners across Asia for a few Rupees – significantly cheaper than cigarettes.[2] It has caused a massive surge in the popularity of areca products and, as there is poor labelling, the tobacco content.

A report appearing in the Economist found that areca products represented an industry worth 10 billion dollars in India alone in 2012.[3] The global production of areca was estimated to be nearly 0.8 million tonnes in 2009 with over 55% of this production from India, and 25% from China. Furthermore the industry provides employment to many millions, including over 30 million people in India. Despite its harmful effects, the growth in consumption and production are mirrored at a growth rate of about 4% annually, suggesting that the habit is far from being in decline.[4]

So what is it about areca that makes it so popular? Studies have shown that areca is as addictive as heroin and have demonstrated an areca dependency syndrome in chronic chewers.[5] Its stimulant properties make it popular with those who need to stay awake – drivers, labourers and factory workers all use areca in societies where a double espresso or a Red Bull would be an unaffordable luxury. However, the heroin-like dependency is just one of its many dangers. Reports also show that in India there are over 5 million children under the age of eight who are addicted to areca-related products.

The main threat is that areca nut is an independent risk factor for head and neck cancer (see Figure 2).[6] [7] [8]

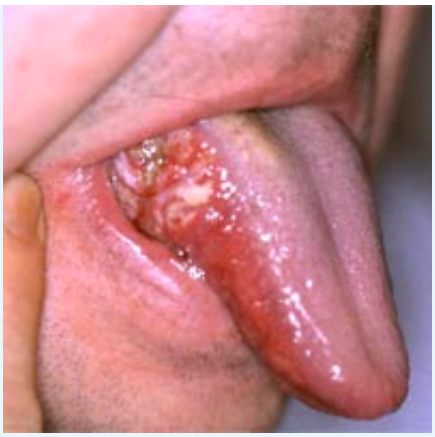

Figure 2: Patient with oral cancer. *(Image by Welleschik)*

Head and neck cancer has been described as an epidemic across South and East Asia (see Figure 3), with approximately 70,000 new cases in India every year. The prognosis is poor, due to late detection, and head and neck cancer is responsible for ~48,000 deaths across India.[6] Rates of oral squamous cell carcinoma in countries such as India are the highest in the world. Oral submucous fibrosis (OSF) is an areca-related pre-cancerous condition that results in patients only being able to open their mouth by a few millimetres. Eight percent of patients undergo malignant transformation.[9] There is still no cure for this condition since its discovery in South Africa in 1952. The author's discovery over a decade ago that high levels of copper in the nut causes an up-regulation of the enzyme lysyl oxidase is a still a front runner in the race to explain this enigmatic disorder.[10] [11]

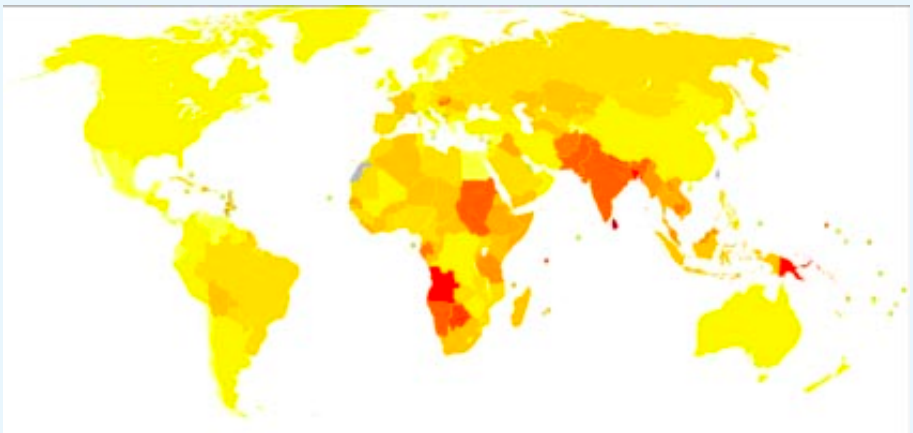

Figure 3: Age-standardised death rates from Mouth and oropharynx cancers by country (per 100,000 inhabitants). *(Image by Lokal_Profil, CC-BY-SA-2.5)*

So what is the future for this not so healthy nut? In many countries in South and East Asia, areca consumption remains a scourge of society and despite attempts to legislate and even ban it, sales continue to surge. Compared to smoking and alcohol, areca has received a fraction of the attention attributed to other public health issues in developing countries and has largely remained under the radar for public health researchers in the West, making this a tough nut to crack!

-- Dr Chet Trivedy, NIHR Academic Clinical Lecturer in Emergency Medicine, W-CAHRD

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CLAHRC WM Quiz

Who developed a system of triage based solely on severity, not status (e.g. army rank) or nationality?

Email CLAHRC WM your answer.

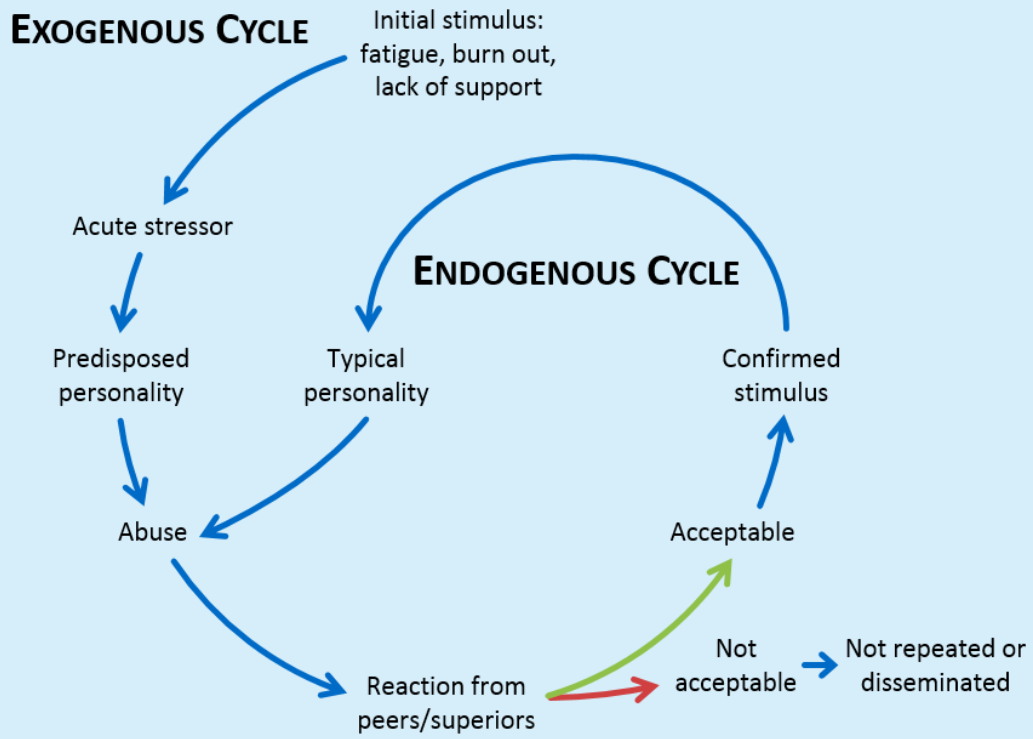
Answer to our previous quiz: Dr Joseph Goldberger identified that **diet** was the cause of Pellagra, specifically lack of vitamin B3, niacin. Goldberger noted that while it was **common in prisoners, it was not common in guards**, and therefore could not have been an infectious disease. He confirmed this by comparing inmates fed a corn-based diet, with ones fed a diet of fresh meat, milk, and vegetables – those on a high corn-based diet had a greatly increased risk of developing pellagra. Read more online.

Congratulations to Alan B. Cohen, Wayne Gillett, and Kate Hill, who were first to answer.

Director's Choice - From the Journals

Care that is Not Just Unskilled but Abusive

Maternal care is disrespectful to the point of abuse in many of the countries of the world.[1] How can it be that members of the caring professions can so abuse their position of trust? This short editorial argues that a culture of poor care can develop among perfectly ordinary people – indeed, we know this from the iconic experiments of Zimbardo [2] and Milgram.[3] As the Good Samaritan experiment shows,[4] people are exquisitely sensitive to their environment, especially their social environment.[5] So, here is my model for how an abusive culture develops:



-- Richard Lilford, CLAHRC WM Director

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References

…And While Talking About Culture and Misbehaviour

A recent Lancet editorial addresses the retraction by BioMed Central of 42 articles published by medical researchers in China.[1] The fraudulent articles emanate from prestigious centres in many parts of the country. This information furnishes a possible explanation for the finding that effectiveness studies that provide null results in North America often provide positive results in China.[2]

-- Richard Lilford, CLAHRC WM Director

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References

Demographic Dividend Divided

Readers of the CLAHRC WM News Blog will be familiar with the concept of the demographic dividend – the opportunity for economic growth when the dependency ratio improves as a result of falling birth rates and before it declines due to an increasing proportion of elderly people. Asian prosperity has been fueled, at least in part, by favourable dependency ratios. However, distorted sex ratios at birth from the usual 105:100 to about 116:100 (males to females) is now resulting in a

mismatch in early adulthood and consequent declining marriage rates. This mismatch accumulates over decades and will lead to a 30% imbalance within a few decades – the mathematics were explicated in more detail in a recent article of the Economist.[1] The situation is further aggravated by the "flight from marriage" as more well-educated women delay or eschew the idea of committing themselves to one man. The social effects of all this are hard to foresee, but it is well known that single men are a restless lot, prone to violence and available for army conscription.

-- Richard Lilford, CLAHRC WM Director

Leave a comment

Reference

Further Evidence from Informal Settlements

At last slum health, featured in previous blogs, is starting to receive the attention it deserves. A recent report on the Mathare settlement in Nairobi, Kenya [1] correlates how far a person lives from a public toilet and risk of disease. The further a person lives from the facility, the more likely they are to be chronically unwell, especially with diarrhoeal diseases and childhood stunting. As readers know, poor nutrition and sanitation create a vicious circle. Also, the risk of violence against women rises with distance from a public facility. Clean water and sanitation remain huge challenges for slum dwellers. Improved sanitation would also produce an educational and economic dividend. Meanwhile toilet design has improved, for example, with the invention of the composting toilet, so cost-effective, logistically feasible improvements are possible and likely to be highly cost-effective. The CLAHRC WM Director liked this paper because it integrated disease surveillance, geospatial mapping, and the personal accounts of slum dwellers, to create a rich account of pathways to poor health.

-- Richard Lilford, CLAHRC WM Director

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Patient and Public Involvement

PPI in Theme 1, Maternity & Child Health

The Maternity team within Theme 1 has three nominated PPI representatives who are invited to relevant research meetings (e.g. theme steering committee). We have established a maternity-specific PPI / academic forum, where we invite representatives to be involved in the design of specific projects (commenting on, and

contributing to the development of protocols, patient documentation, and implementation plans). We also plan to involve our PPI representatives in the delivery of projects themselves where possible, e.g. inviting PPI reps to participate in co-production workshops for place of birth discussion with midwives.

Additionally, the Child Health team is concerned with ensuring that young people are also actively involved. As suitable young people were not recruited through the main CLAHRC WM recruitment process, we are exploring further involvement with the Clinical Research Network consumer liaison officer for children and young people, and with Birmingham Children's Hospital NHS Foundation Trust's patient liaison officer. We also consult with the BCH Young Persons Advisory Group on our proposed research, most recently concerning their perspective on a proposed evidence synthesis application on the mental health of young people with chronic conditions.

PPI Internships

As part of efforts to embed PPI more firmly in research, CLAHRC WM is planning to offer our PhD students the opportunity to undertake a **PPI Internship** to better understand the role of PPI in health service delivery research. We have a number of 'PPI Professionals' willing to provide shadowing placements to offer insights and also some specific PPI projects. For example, a survey of stakeholders to gain feedback on the informed consent processes for the Birmingham Genomics Medicine Centre.

If you are a PhD student, or you know someone who might be interested in the PPI Internship scheme, please get in touch with Nathalie Maillard on n.maillard@warwick.ac.uk for further information.

International Clinical Trials Day 2015

This year's International Clinical Trials Day is on Wednesday 20th May, and the NIHR will be promoting it's "OK to Ask" campaign to encourage patients and the public to ask medical professionals about clinical research.

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Selected Replies

Re: Use of Language: Race is to Ethnicity as Sex is to Gender

I've always thought that gender is what you are – male/female, and sex is what you do. And no they are not interchangeable. When I review documents I revise accordingly – seems I am wrong?!

-- Andrew Entwistle

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Personality of the Issue

Dr Sarah Flanagan

Sarah Flanagan is an Honorary Research Fellow working on CLAHRC WM Theme 4, Chronic Diseases at the University of Birmingham.

Sarah obtained her BA in Philosophy and Literature from the University of Warwick in 1994, and spent ten years working in the voluntary and statutory sector (BSMHFT) in the field of addictions. In 2004 she gained a MA in Philosophy and the Ethics of Mental Health, and in 2006 joined the University of Birmingham to pursue a Research Support Facility fellowship. She spent two years as a Research Associate working on various projects, including a study examining the barriers and facilitators for 'hard to reach' groups accessing health and social care services. In 2012 Sarah completed a Cancer Research UK funded PhD looking at the adverse outcomes of undergoing a colposcopy. Following this, she spent a year as a Research Fellow on a project exploring data methods collection utilised with teenagers and young adults with cancer.

She is currently involved in four projects based at the Heart of England NHS Foundation Trust. One project is an evaluation of enhanced care pathways for older patients admitted with major trauma, and three projects are related to patients undergoing lung surgery.

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News

Job Opportunities

Research Fellow (Warwick Medical School)
Based at Malawi-Liverpool Wellcome Trust Clinical Research Programme, Blantyre,

Malawi
£28,695 - £37,394
6 months fixed-term contract
Closing: 13th May 2015

An opportunity to undertake research in Blantyre, Malawi as part of Warwick Centre for Applied Health Research and Delivery (W-CAHRD) to assist in the successful execution of research projects aiming to improve the health of populations in low- and middle-income countries.

For an informal chat about the position, please contact Prof Richard Lilford, r.j.lilford@warwick.ac.uk or Jo Sartori, j.sartori@warwick.ac.uk. For more information, and to apply, click here.

Assistant Clinical Studies Coordinator (5 posts)
Keele University
Grade 6 (starting salary £25,513)
One year fixed-term post, full-time
Closing: 10th May 2015

The Keele Clinical Trials Unit is based in the Research Institute for Primary Care & Health Sciences. As part of the CTU team, and working in collaboration with nominated research groups, the post holder will assist in the co-ordination of clinical studies undertaken within the Keele CTU.

For full details and to apply, please visit: http://tinyurl.com/SE15-34
Post reference: SE15/34

Research Fellow: Arthritis and Long-Term Conditions
Keele University
Grade 8 (starting salary £39,685)
Five years fixed-term post, full-time
Closing date: 23rd May 2015

The overall aim of this post is to work with the multidisciplinary research team to support the delivery of studies relevant to musculoskeletal problems in primary care, directly linked to the NIHR Research Professor of General Practice's programme of research. If you would like to discuss this position further, please do not hesitate to contact Professor Christian Mallen (c.d.mallen@keele.ac.uk)

For full details and to apply, please visit: http://tinyurl.com/RE15-08
Post reference: RE15/08

New W-CAHRD Website

The Warwick Centre for Applied Health Research and Delivery (W-CAHRD) have launched a new website and Twitter feed: @Warwick_CAHRD. W-CAHRD is a global network that brings together individuals, disciplines, and organisations to develop practical solutions to health needs. In particular, they work with resource-limited nations to transform health systems and improve the health of those in low- and middle-income countries.

Online Attention for Paper on Stepped Wedge Studies

A recent BMJ paper by Hemming et al. on stepped-wedge cluster randomised trials, (*BMJ*. 2015; 350: h391), has been ranked by Altmetric as being in the top 5% of all articles tracked according to online attention received. Do let us know of any other CLAHRC WM publications that have been getting noticed online.

London Marathon Congratulations

Congratulations to Tom Marshall (CLAHRC WM Deputy Director) who ran a personal best in the 2015 London Marathon, finishing in 3h 05' 33" (an average pace of 7 minutes a mile).

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Events

1-2 Jul 2015
HSRN Symposium
Nottingham Conference Centre

Involved in Health Services Research? The Health Services Research Network (HSRN) is hosting their annual HSRN Symposium, 1-2 July 2015 in Nottingham. This provides the ideal opportunity for you to hear and discuss cutting edge health services research.

This year's Symposium will showcase landmark evidence on stroke services reconfiguration, and discussions on data futures and the challenges facing the NHS post-election. A plenary discussion will offer first impressions from the international round table evaluating service and system innovations in health care and public health. There will also be a birthday celebration of 20 years of the Journal of Health Services Research and Policy.

Strand sessions will address workforce, self-care, developing interventions, quality, patient experience, and improvement science with additional sessions looking at systems modelling (Martin Pitt & colleagues), the researcher in residence model, and emergency admissions (Alicia O'Cathain and colleagues).

The Symposium provides the ideal opportunity to hear and discuss current issues and potential new methods to improve health services and patient care. Come and listen, have your say, make your opinion count, and network with some of the leading health services researchers in the UK and internationally. Find out more online.

8-10 Jul 2015
44th Annual Conference of the Society for Academic Primary Care. Evidence and Innovation in Primary Care.
University of Oxford

This regular meeting is the UK's largest and most well-established primary care conference, held in partnership with the University of Oxford's Nuffield Department of Primary Care Health Sciences. It typically attracts around 350 GPs and researchers to discuss the latest research and education to advance primary care. Presentation abstracts can still be submitted until 10:00am, 23rd February. Further details can be found online.

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Publications

Flanagan SM, Greenfield S, Coad J, Neilson S. An exploration of the data collection methods utilised with children, teenagers and young people (CTYPs). *BMC Res Notes*. 2015; **8**:61.

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Roughley MJ, Belcher J, Mallen CD, Roddy E. Gout and risk of chronic kidney disease and nephrolithiasis: meta-analysis of observational studies. *Arthritis Res Ther*. 2015; **17**(1): 90.

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