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ARC West Midlands News Blog



24 January 2020

Measuring Things That Are Not Themselves Directly Observable

*Richard Lilford, ARC WM Director
Timothy Hofer, Professor of General Medicine*

Much of science concerns concepts, not material entities. We talk easily and glibly about wealth, satisfaction, liberal democracy and metropolitan elites. But in science we need to quantify these types of thing. To paraphrase Galileo; if something is not measurable make it so!

The ARC WM Director was made very aware of definitional and measurement issues while attending the African Research Collaboration on Sepsis research meeting in Dar Es Salaam. The Collaboration is funded by an NIHR Global Health Group grant awarded to Jamie Rylance at Malawi Liverpool Wellcome Research Centre. The meeting covered many fascinating topics. One recurring theme was how to define sepsis. Since 1991, three international conferences have been held to “define sepsis” – the most recent consensus statement (2016) was published in JAMA.[1]

Right off the bat in reading the literature there is a problem, as the challenge of the measurement task is often referred to as that of finding an operational definition or worse simply “a definition”. This is a problem because referring to the measurement task as “defining sepsis” can obscure the fact that there is currently a well specified and seemingly widely accepted conceptual definition of sepsis from Sepsis-3, namely “Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.”[1] But as noted in the same publication, “There are, as yet, no simple and unambiguous clinical criteria

or biological, imaging, or laboratory features that uniquely identify a septic patient.” So, to be clear, virtually all of the arguments and difficulties that have arisen after each consensus conference establishing a conceptual definition are in how to design a measurement procedure, including the selection of a population, a set of observable variables and the mathematical model that combines them. So this got us thinking about measurements of scientific constructs.

A clearly defined conceptual entity that is not directly observable is often referred to as a latent construct or variable. Building on Bollen and Bauldry,[2] and Hand,[3] three scenarios are possible when defining a measurement procedure for a latent construct, such as ‘sepsis’:

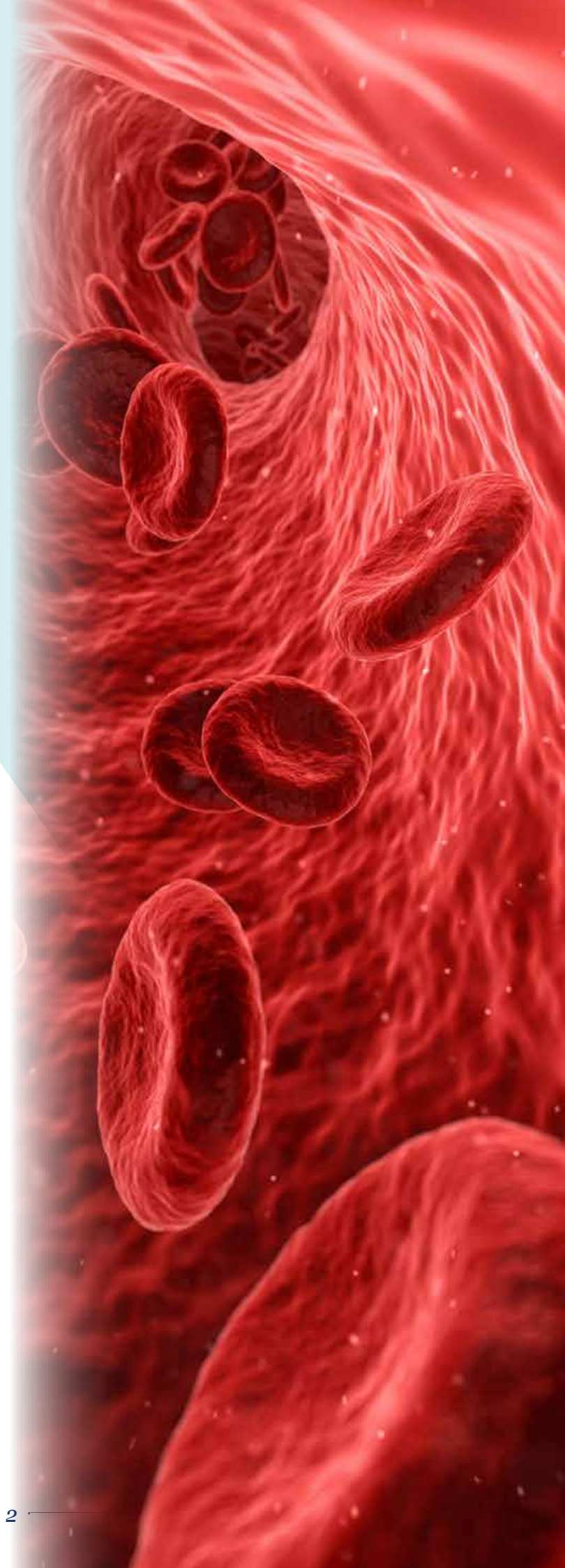
① Where a measurable reference category or gold-standard for a latent construct exists, such as the molecular classification of intersex or the chemical classification of endocrine disorders. The reference category is then held to be the observable representation of the construct. Other potentially more easily measured observable features can be assessed directly as to how accurately and precisely they represent the construct through their relationship to the reference category.

② Where theory is “poorly formulated” with regard to how the latent construct exerts its effects, some observable features can be combined in what Hand called a “pragmatic measurement”[3] procedure to produce a

measurement that is useful not because you understand what is going on but only to the extent that the pragmatic measures have some ability to predict an outcome of interest, as is the case with the concept of socioeconomic status, the histological grading of tumours, or the APACHE score of acute illness severity. In the absence of a model causally relating the construct to the observed features, the combination of the features into an index can only be said to summarise the observable features rather than represent the underlying construct. In turn, the index is actionable only because of its ability to predict. Finally, as the index is only a summary of observable features, the components of such an index cannot be changed without changing the nature of what is being measured.

3 Where there is a well-specified formal conceptual definition the task is to identify a pool of exchangeable and observable features that theory would suggest are caused by the construct. By use of a statistical model that includes those observable features, the latent variable that causes them can then be identified. Yet, the hypothesised causal relationship between the underlying construct and the observed effects requires a continuing effort to collect evidence supporting the argument that the observed effects are a valid representation of the underlying construct. The example here would be schizophrenia, where the American College of Psychiatrists definition has allowed the science to proceed. A latent social construct ('this is a schizophrenic') is hypothesised to predict the observed clinical manifestations that can be measured. This measurement model is itself a theory that remains open to revision or being abandoned entirely, but which still can be employed as a useful tool.

In our opinion the latter 'third way' is appropriate for 'sepsis'. The conceptual definition is not, cannot be, perfect but it is based on broad consensus. Once the conceptual definition has



crystallised, science can proceed to develop one or more measurement procedures. These measurement procedures may well need to be refined or changed in different settings of care. The research may one day yield a reference standard reflecting basic mechanisms; possibly this point is within reach in the case of schizophrenia, where genome-wide association studies have yielded stunning findings.[4] We think this is the approach the sepsis field should

follow. It is more profitable than devoting endless effort to attempting to find the holy grail of a reference standard for sepsis. It seems reasonable to accept the JAMA proposal for an operational measurement of the construct. While using it, continue to collect evidence that supports or refutes the theory represented in the measurement model.

References:

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016; **315**(8): 801-10.
2. Bollen KA, & Bauldry S. Three Cs in Measurement Models: Causal Indicators, Composite Indicators, and Covariates. *Psychol Methods*. 2011; **16**(3): 265-84.
3. Hand DJ. Measurement theory and practice: the world through quantification. London: Wiley-Blackwell; 2004.
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ARC WM Quiz

Which **French obstetrician**, who died in 1957, gave his name to a method of childbirth involving exercises and breathing control designed to give pain relief without drugs?

email your answer to:
ARCWM@warwick.ac.uk



Answer to our previous quiz: The ventouse was invented in the 1950s by **Tage Malmstrom**, a Swedish obstetrician, based on work by Sir James Young Simpson in 1849.

Mendelian Randomisation Studies: an Excellent Primer from the BMJ

Richard Lilford, ARC WM Director

News blog readers know that I am a fan of Mendelian randomisation studies. Much better than observational studies and second only to an experiment of a type that is often hard to do with sufficient precision. Some of my colleagues are less enamoured, worrying that they are over-interpreted. The BMJ has featured many meticulously reported studies where Mendelian randomisation is used to create an ‘instrument’ for cause/effect inferences. Many of these have been reported in our predecessor NIHR CLAHRC West Midlands News Blog (see Table).

It is timely that the BMJ has now published an excellent guide to responsible use of this type of instrumental variable.[7] The paper describes the single and merged study approaches and tests for horizontal pleiotropy (whereby the genetic variant

Genes associated with...	Are associated with...	Ref
High educational attainment	Reduced risk of Alzheimer’s disease	[1]
High density lipoproteins	Reduced coronary risk	[2]
Triglycerides	Increased coronary risk	[3]
Years spent in formal education	Reduced coronary heart disease	[4]
High testosterone levels	Increased cardiovascular risk	[5]
Long hours spent in the classroom	Myopia	[6]

may violate the exclusion assumption because it can bypass the putative explanatory variable). One thing that I learned was the potential for time to interact with genes. For instance, genetic influences may operate only at specific times. For example, Mendelian randomisation involving genetic variants for vitamin D metabolism corroborate studies of an association between low levels of vitamin D and multiple sclerosis. However, vitamin D only provides protection at early ages. This point about life time effects of exposure

can make it harder to estimate the magnitude of an effect than the direction of effect.

Mendelian randomisation is an important tool in modern epidemiology and no-one can really call themselves an epidemiologist without nuanced knowledge of the subject. In terms of causal inference it occupies a status intermediate between standard observational methods and RCTs. And like **all** methods it should be close-coupled with theoretical knowledge, as we argue repeatedly in this News Blog.

References:

1. Larsson SC, et al. [Modifiable pathways in Alzheimer’s disease: Mendelian randomisation analysis](#). *BMJ*. 2017; **359**: j5375.
2. Do R, et al. [Common variants associated with plasma triglycerides and risk for coronary artery disease](#). *Nat Genet*. 2013; **45**(11): 1345-52.
3. Frikke-Schmidt R, et al. [Association of loss-of-function mutations in the ABCA1 gene with high-density lipoprotein cholesterol levels and risk of ischaemic heart disease](#). *JAMA*. 2008; **299**(21): 2524-32.
4. Tillmann T, et al. [Education and coronary heart disease: Mendelian randomisation study](#). *BMJ*. 2017; **358**: j3542.
5. Luo S, et al. [Association of genetically predicted testosterone with thromboembolism, heart failure, and myocardial infarction: mendelian randomisation study in UK Biobank](#). *BMJ* 2019; **364**: 1476.
6. Mountjoy E, et al. [Education and myopia: assessing the direction of causality by mendelian randomisation](#). *BMJ*. 2018; **361**: k2022.



NIHR Standards for Involvement: ARC WM's Approach to Working with Standards

Magdalena Skrybant, Public Involvement Lead ARC WM

On 18th November 2019, the NIHR launched its *Standards for Involvement*. These are designed to provide 'clear, concise benchmarks for effective public involvement alongside indicators against which improvement can be monitored'. Six standards were developed over three years by a team of UK partners, and each was piloted by Test-Bed sites (including Keele University's Research User Group) and 'Free-Stylers', which included CLAHRC WM's Public Advisory Group.

What are the Standards?

The Standards encourage anyone involved in public involvement activities to consider what 'good' involvement might look like and how practices can be improved. The Standards are summarised here, while the full version can be accessed at:

http://engage.hscni.net/wp-content/uploads/2019/11/UK-Standards-for-Public-Involvement_Nov19.pdf

Inclusive Opportunities

Offer public involvement opportunities that are accessible and that reach people and groups according to research needs.

Working Together

Work together in a way that values all contributions, and that builds and sustains mutually respectful and productive relationships.

Support and Learning

Offer and promote support and learning opportunities that build confidence and skills for public involvement in research.

Communications

Use plain language for well-timed and relevant communications, as part of involvement plans and activities.

Impact

Seek improvement by identifying and sharing the difference that public involvement makes to research.

Governance

Involve the public in research management, regulation, leadership and decision making.



How will we be using the Standards?

ARC WM is in the very fortunate position of being able to draw on experiences from CLAHRC WM of using the Standards to reflect on its public involvement. CLAHRC WM held workshops with public contributors, researchers and CLAHRC WM's central team in January 2018 and July 2019 to consider what was working well, what wasn't working well, and how practices could be improved in public involvement. The Standards provided a useful framework and discussions ranged from offering very specific practical suggestions to grand visions for involvement. Feedback was honest and constructive and shaped our approaches to public involvement in ARC WM.

ARC WM hopes to replicate the positive experiences of using the Standards as a framework to reflect on public involvement activities. ARC WM has made a commitment to:

- Hold a Standards workshop in year one to explore what 'good' might look like in public involvement. The workshop would involve researchers, public contributors and members of the Central Management Team.

- Hold an annual Standards workshop, providing an opportunity to see how practices have improved and where further improvements can be made.

As public involvement lead, I make sure that the Standards form part of the induction for public contributors and training for researchers.

The Standards document has the following strap-line: *'Deliver better public involvement for better health and social care research'*. We certainly hope that our commitment to working with the Standards will help us achieve this vision.



Burnout Among Doctors: Seed or Soil

Richard Lilford, ARC WM Director

News Blog reader Alastair Sterling drew my attention to a report on doctor burnout across OECD countries.[1] Burnout rates were high everywhere, but not particularly so in the UK. It was hard to make comparisons, because the survey was based on respondents who might have differed from place to place. Some studies have indeed compared different members of the workforce with respect to burnout rates. A number of studies have shown that physicians have higher burnout rates (along with other sorts of psychological

morbidity) than other groups. A recent perspective on this subject in the Lancet referred to a 2012 study saying,

“the risk of burnout decreased with each additional higher level of education... the only outlier was a degree in medicine that instead increased burnout risk by 36%.”[2][3]

Of course, this does not clarify whether the problem lies with the particular demands of

medical practice or a lack of resilience among people who choose to go into medicine. While there is no irrefutable evidence on this point, people going into medicine do *not* have higher levels of vulnerable psychologies than their peers. If anything, the evidence points the other way and people who are accepted into medical school tend to have better baseline quality of life than other students.

Medical practice does produce some particular and unrelenting forms of stress. Encounters with clients are

intense, and the responsibility unrelenting. Stress is an ineluctable part of medical practice. Doctors have to deal with extensive bureaucratic pressures and the demands of inflexible information systems. While all professions have to deal with IT, the contribution of IT to burnout among both US and British doctors has been featured in a previous News Blog [4] and in Bob Wachter's brilliant book on the digital doctor.[5]

It seems that the problem of burnout among doctors is very real. Some of its causes are difficult to eliminate – the psychological pressure of dealing with sick people and their worried families can never go away. However, better management and organisation, and a more realistic set of expectations, might go some way to preserving the health of the people who look after other people's health.

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1. Medscape. Global Physicians' Burnout and Lifestyle Comparisons. 2019
2. Marchalik D. Physician Burnout in the Modern Era. *Lancet*. 2019; **393**: 868-9
3. Shanafelt TD, Boone S, Tan L, et al. Burnout and Satisfaction With Work-Life Balance Among US Physicians Relative to the General US Population. *Arch Intern Med*. 2012; **172**(18):1377-85.
4. Lilford RJ. How Many Doctors Do We Really Need? NIHR CLAHRC West Midlands News Blog. 29 January 2016.
5. Wachter R. The Digital Doctor: Hope, Hype, and Harm at the Dawn of Medicine's Computer Age. New York, NY: McGraw-Hill Education. 2015.





Yet Another Trial of Mineral and Vitamin Supplements with a Null Result: This Time Involving Male Fertility

Richard Lilford, ARC WM Director

Whenever the ARC WM Director sees the title of a randomised trial, he tries to predict the findings. When he sees a trial of vitamin and mineral supplementation in otherwise healthy people, he predicts a null result. This is exactly what happened when he came across a trial of zinc and folic acid supplementation to promote male fertility, recently published in JAMA.[1] Sure enough, the supplements had no effect on either fertility rates or semen quality.

Why were these two agents selected for evaluation? Apparently seminal fluid is very rich in zinc, while folic acid and

zinc often act synergistically. However, discerning News Blog readers will immediately spot that this is a very facile argument. It is akin to the risible conclusion that because bones contain calcium, calcium can prevent osteoporosis in people who are not calcium deficient. However, vitamin and mineral supplementation is a large industry and human beings have been beguiled by simplistic remedies throughout our evolution. Expect many more boring trials of vitamin and mineral substitution. If I had more time on my hands, I would carry out a multiple indication review across all vitamin and mineral substitution types to establish,

once and for all, that vitamins and minerals should not be given to people who are not vitamin or mineral deficient. A possible exception is iron, because humans have no method to excrete iron and therefore absorb iron badly.

Reference:

1. Schisterman EF, Sjaarda LA, Clemons T, et al. [Effect of Folic Acid and Zinc Supplementation in Men on Semen Quality and Live Birth Among Couples Undergoing Infertility Treatment. A Randomized Controlled Trial.](#) *JAMA.* 2020; **323**(1): 35-48.



Pre-eclampsia and Risk of Vascular Dementia, and Older Dads

Richard Lilford, ARC WM Director

Pre-eclampsia, for all that it is a disease of the first pregnancy, is a vascular disease. It is associated with vascular complications later in life, including hypertension and stroke. *STOX1*, a pre-eclampsia susceptibility gene, is over-expressed in late Alzheimer's disease. It is therefore natural to ask whether pre-eclampsia is associated with dementia in later life. Previous studies have been rather underpowered. Now a massive data base study of over a million pregnancies has reported from Denmark. [1] A strong association was found between pre-eclampsia and vascular dementia (hazard ratio over three and over six for severe cases) but the hazard ratio was much lower for Alzheimer's disease. This confirms the association between pre-eclampsia and blood vessel disease, and

the weak association with Alzheimer's disease may be the result of misclassification.

My wife reminds me that I told her that I wanted to complete my family by the age of 40. Anyway I was largely correct. A massive registry study of over 40 million pregnancies in the US shows that the babies of older dads are more likely to be born prematurely, have seizures and be small for gestational age (after correcting for mother's age) than the progeny of younger men.[2] And the mothers were more likely than those of younger men to have gestational diabetes. These effects likely result from gene imprinting as a fellow ages. It has been known for over a century that old dads are also more likely than young ones to have children with genetic

defects due to accumulation of genetic mutations in older sperm. Of course this should not preclude older men from having children – there are always risks in life and a loving dad can more than compensate in all but a very few cases.

References:

1. Basot S, Wohlfahrt J, Boyd HA. [Pre-eclampsia and risk of dementia later in life: nationwide cohort study.](#) *BMJ.* 2018; **363**: k4109.
2. Khandwala YS, Baker VL, Shaw GM, Stevenson D, Lu Y, Eisenberg ML. [Association of paternal age and perinatal outcomes between 2007 and 2016 in the United States: population based cohort study.](#) *BMJ.* 2018; **363**: k4372.



Unexpected Costs of Charity Fundraising

Peter Chilton, Research Fellow

At some point most of us have sponsored a friend or colleague planning to perform a challenging feat, such as skydiving or abseiling down an office block, in order to raise money for a charity. However, these feats are challenging for a reason, coming with a significant health risk. News Blog reader Oyinlola Oyebode recently drew our attention to an interesting paper looking at the health cost of parachuting for charity.[1]

The authors looked at all parachute-related injuries at two local parachute centres over a five-year period, and found that 94% of the 174 recorded injuries were first-time parachutists being sponsored for charity. They estimated that this figure amounted to 11% of all charity-parachutists over the period. Of this, 63% were admitted to hospital, giving a 7% rate of serious injury. Those admitted to hospital cost the NHS an average of £5,781, while the average cost for those treated as outpatients or in A&E was £265.

Overall, the average cost per charity-parachutist injured was £3,751. Unfortunately, the average amount raised per person, after expenses, was £30, meaning that for each £1 raised for charity, the NHS spent £13.75 on healthcare.

Reference:

1. Lee CT, Williams P, Hadden WA. [Parachuting for charity: is it worth the money? A 5-year audit of parachute injuries in Tayside and the cost to the NHS.](#) *Injury Int J Care Injured.* 1999; **30**: 283-7.



On Corruption

Richard Lilford, ARC WM Director

Consider the equation:

$$B_p > C_{psy} + pp (C_{crim} + C_{soc}) + C_{fav}$$

“In this equation, B_p represents the perceived benefit of an act of corruption, C_{psy} the psychological costs, pp the perceived probability, C_{crim} the criminal costs, C_{soc} the social costs to the individual, and C_{fav} the costs of doing the corrupt act.” [1]

An interesting and very well written article in the Lancet by Patricia Garcia tackles the problem of corruption in global health.[1] She outlines the enormous extent of the problem and describes the huge costs to society of rampant, endemic corruption. She also outlines the many and various forms that corruption can take, from absenteeism to diversion of funds.

The earlier equation suggests that the problem must be tackled at many levels. Importantly, care providers and managers need to resist temptation and behave with high rectitude. The personal psychological cost of engaging in corruption is high for high rectitude people. However, corruption can become institutionalised and part of the culture. In that case, it is not possible to rely on individuals and the culture has to be changed and dis-incentives must be introduced.

People sometimes excuse corruption on the basis of poverty and poor pay. Yet News Blog readers might remember a study in which higher pay for the police did not reduce the amount of money collected illegally.[2] The Author calls on more research into the prevention of corruption.

References:

1. Garcia PJ. [Corruption in Global Health: the Open Secret](#). *Lancet* 2019; **394**: 2119-24.
2. Foltz JD, Opoku-Agyemang KA. [Do higher salaries lower petty corruption? A policy experiment on West Africa’s highways](#). London, UK: International Growth Centre (IGC); 2015.



Latest News

Co-funded ARC Studentships

Three ARC-WM co-funded PhD studentships are currently available. Two are at Warwick Medical School, and can be viewed at: warwick.ac.uk/fac/sci/med/about/centres/arc-wm/news-events/latest-news/?newsItem=8a17841b6f85aa19016f8ab5602e1794.

The third is at Warwick Business School: warwick.ac.uk/fac/sci/med/about/centres/arc-wm/news-events/latest-news/?newsItem=8a1785d76ef04032016f143c51123ee1. The closing date for applications is **Monday 27 January 2020**.

The NIHR are looking to appoint members to the Programme Grants for Applied Research (PGfAR) committee, in particular applied health, public health or social care researchers with experience of running trials and using diverse methodologies to demonstrate patient,

service user or carer benefits. The closing date for applications is **Friday 31 January 2020**. For more information, and to apply, please see: nhr.ac.uk/vacancies/programme-grants-for-applied-research-subcommittee-membership/22469.

PROMs Conference

The fifth national Patient Reported Outcome Measures (PROMs) conference is being held on Wednesday 10 June 2020 at the University of

Sheffield. To register your interest, please email: ARC_HEEE@sheffield.ac.uk.

Are Friends Bad For Your Health?

Dr Oyinlola Oyebode, University of Warwick, was recently commissioned to write an article for the BBC on the effect our friends can have

on our health. It can be viewed online at: www.bbc.co.uk/news/health-49368842.

Essential Guide to Grant Applications

The [NIHR Research Design Service South Central](http://NIHR_Research_Design_Service_South_Central) recently held a masterclass on how to write strong grant applications, and have

published 16 plenary teaching sessions on their YouTube Channel: youtube.com/playlist?list=PLquUPB8ibcKlX5aPOVnF_1oddIHk8NvWY

Registration for the Qualitative Health Research Network training programme, taking place 2-4 March 2020 in London, is now open. The programme is being run by University College London and three courses are being offered on introduction to:

QHRN Training Programme

- Rapid Qualitative Research (2 March)

- Rapid Evaluations (3 March)
- Ethnography (4 March)

For more information, and how to register, please visit: ucl.ac.uk/qualitative-health-research-network/training-programme

Latest Funding Opportunities

Efficacy & Mechanism Evaluation programme

19/159 [Injuries, accidents and urgent and emergency care](#)

20/04 [Building Clinical Trials Experience](#)

Public Health Research programme

19/164 [Injuries, accidents and urgent and emergency care](#)

HS&DR programme

19/165 [Injuries, accidents and urgent and emergency care](#)

20/02 [Researcher-led \(standard\)](#)

20/03 [Researcher-led \(evidence synthesis\)](#)

HTA programme

19/160 [Researcher-led \(primary research\)](#)

19/161 [Researcher-led \(evidence synthesis\)](#)

19/162 [Injuries, accidents and urgent and emergency care \(primary research\)](#)

19/163 [Injuries, accidents and urgent and emergency care \(evidence synthesis\)](#)

Selected Replies

Re: [Why Are University Students so Depressed?](#)

2019;**1**(2):1-3.

Here is a sixth hypothesis: decline of religion.

a) What is the meaning of life? If there is no grand plan, suffering is just suffering.

b) When someone dies they are gone forever, they are not watching over you and you'll never be re-united.

c) Lust used to drive commitment (since sex

was only within marriage) but now young people find it hard to get other young people to commit to them (so feel worthless and alone). Plus courting (without sex) is not the emotional rollercoaster of finding new and breaking-up sexual relationships.

-- *Oyinlola Oyebode, Associate Professor in Public Health*

I read the ARC WM's recent blog, in particular the article on depression in university students. Another couple of ideas that I have on this topic are that for some students, excessive alcohol consumption could be adding to the issue. Thinking back to my university days, drinking heavily was encouraged by peers and tolerated/facilitated by universities (through student unions/college bars/social events). I understand

that alcohol consumption is decreasing in younger age-groups, but I imagine this is still a significant factor. In addition, perhaps transition to a new university environment from home/school could be an issue? Clearly, there are challenges associated with transitions at many stages in life, so I imagine that this is a factor too.

-- *Andy Rose*

Recent Publications

- Currie G, Kiefer T, Spyridonidis D. [From What We Know to What We Do: Enhancing Absorptive Capacity in Translational Health Research](#). *BMJ Leader*. 2019.
- Damery S, Sein K, Nicholas J, Baharani J, Combes G. [The challenge of managing mild to moderate distress in patients with end stage renal disease: results from a multi-centre, mixed methods research study and the implications for renal service organisation](#). *BMC Health Serv Res*. 2019;**19**(1):989.
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- Turner G, Aiyegbusi OL, Price G, Skrybant M, Calvert M. [Moving beyond project specific patient and public involvement in research](#). *J R Soc Med*. 2020;**113**(1):16-23.