NIHR | Applied Research Collaboration West Midlands

Volume 4, Issue 10

ARC West Midlands News Blog

28 October 2022

Aqueous-PREP:
a Cluster Cross-Over Trial

Karla Hemming, Professor of Biostatistics

A cluster randomised cross-over trial was published in the Lancet this week, looking at the use of aqueous skin antisepsis before surgical fixation of open fractures (Aqueous-PREP).[1] It included 14 hospitals (the clusters) and every two months hospitals switched between one of two different types of skin antisepsis solutions (the treatments). Around 3,600 eligible patients were recruited – each treated by whichever treatment was standard of care in the period the patient was admitted.

There is great potential for the cluster cross-over trial to be used to test questions around effectiveness of interventions that are in every day use but for which there is no good evidence any one is better (such as for skin antisepsis solutions). However, some caution is needed.

Firstly, when participants are recruited in unblinded cluster randomised trials – they are recruited with knowledge of the intervention that they will receive. For example, in Aqueous-PREP, at the time of recruitment, the unblinded nature of the interventions (here the solutions were different colours), means that there is potential to differentially recruit to the different study arms (lack of concealment of allocation). We know concealment of allocation is crucial to the success of RCTs – and that is the case in cluster cross-over trials too. Whilst in Aqueous-PREP there was no clear indication of any differential recruitment (baseline tables looked well balanced) – perhaps we should be more cautious about investing in cluster cross-over trials unless someone goes the extra mile and blinds the treatment conditions.

There are other issues with cluster cross-over trials – namely estimates of effects and their confidence intervals can be biased, particularly in small samples or where there are underlying time effects. Time effects can be important in these study designs – as although the trials are planned to balance on time, this is often not realised in practice. Aqueous-PREP allowed for this by adjusting for "time" – albeit using continuous time – thus making the rather strong assumption that any time effects are linear.

But, perhaps, the most important learning point of this trial, is the reminder not to conflate evidence of absence with absence of evidence: the confidence interval for Aqueous-PREP included both potential for either of the solutions to be superior to the other, yet this was suggested as being evidence of no difference. Solutions to this – larger trials ideally, but in absence of that, a Bayes interpretation can help prevent the misinterpretation of statistical significance that is ubiquitous.

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Limitations of Risk-Scoring Generally and AI in Particular in Clinical Practice

Richard Lilford, ARC WM Director

In a previous news blog [1] I explicated the problem with medical records and the issue of data-wrangling in the unstructured parts of the record in which unfolding of the clinical reasoning process largely takes place. I also documented the decline in belief that machine learning could contribute much to diagnostic reasoning and the consequent loss of value in companies trading in this space.[2] The temptation to analyse the increasingly extensive and accessible clinical databases continues apace in many academic circles. So here I summarise concerns regarding the use of clinical databases generally, and machine learning in particular, when used to inform clinical practice and risk prediction. I pose the problem as a set of questions investigators should ask themselves before proceeding with unbridled enthusiasm.

1 Is the outcome variable well-defined?

Machine learning can outperform experts in chess and the game 'Go',[3] because there is a clear outcome – winner and loser. This is also largely (not completely) the situation with imaging diagnosis – on a large enough selection of chest x-rays the machine will mimic the best clinical diagnostician. If the end-point is determined not by agreement with an expert but with, say, the ultimate histology, then the association will likely be biased because only a minority of x-rays gets referred for a tissue diagnosis – there will be 'survivorship' bias.

2 Is the outcome objective?

If the outcome is self-referential, then AI will replicate any fault in the previous system. The famous example here is machine learning replicating racial bias in crime detection. The literature is replete with examples of spurious associations leading to unstable conclusions.

3 Is the success of the 'machine' all ascribable to the 'machine'?

This problem is similar but not identical to outcome bias. Here, the outcome is more likely to materialise in a context where the information that is collected is itself motivated because the clinician suspects the outcome. This bias flatters machine diagnosis – the clinician collects data (e.g. does a blood culture) *because* they suspect a disease (e.g. sepsis). The machine conditions on the positive test result and gets false credit. This is an example of conditioning on a collider.[4]

4
How and in what way are the treatment variables collected in the database related to those in the population informed by the analysis?

This is my main concern. People seem to find this point hard to follow. So let us take an example. Imagine that all people in population A who have high cholesterol take a fully effective treatment to lower their cholesterol. Then, at the limit, the correlation between high cholesterol and cardiovascular disease will disappear – the 'treatment paradox'. If we extrapolate risk prediction from population A to a treatment naïve population, then the risk of cardiovascular disease will be grossly underestimated. In practice, risk assessment is made with little knowledge of how much exercise, anti-smoking advice and prophylactic treatment, etc is given. Yet, it is supposed to inform individual decisions in different populations where this information is also largely unknown. Thus, the risk prediction is always wrong. It underestimates the natural history and overestimates risks for future populations where prophylactic actions are increasingly adopted over time.

One of the problems with database studies in machine learning is that it is always out of date. While you could say that about any epidemiological research, there is a difference. In the case of standard epidemiological research, the statistical model (should) inform on a causal model. That way, if something has changed in the outside world, it can be taken into account in decision making. For example, when I was a member of the NICE appraisal committee, we considered the effect of statins on stroke recurrence. But the studies were done before widespread adoption of platelet-inhibitors. It was therefore necessary to recalculate the absolute risk reduction from statins, given a new and lower baseline risk due to platelet-inhibitors (assuming independent effects given different mediating mechanisms). With machine learning, you are flying blind.

Databases continue to reveal new knowledge by looking at explanatory variables, mediators and outcomes, as in the fields of pharmaco-epidemiology and molecular genetics. But keep your eyes wide open if you are looking for new associations or developing prediction models with old risk markers. And be very circumspect regarding machine learning. A recent systematic review found only 45 randomised trials of machine learning in medicine,[5] most dealing with specific diagnostic procedures and generally of sub-optimal quality. It would seem that the day when a machine can scan an electronic health record to provide a diagnosis that the doctor has not thought of, is a long way off. To think that this methodology is just around the corner, is magical thinking.

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Looking Around Corners:
Emerging Trends in Health Research

Richard Lilford, ARC WM Director

The WHO defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".[1] This declaration impoverishes language, since we need a vocabulary that allows us to succinctly describe the absence of disease. Such a definition does not imply that there is nothing of importance beyond the absence of disease. A more philosophically grounded approach is to simply recognise that humans seek many objectives beyond health. My point is purely linguistic, since the notion that health researchers should look beyond health and that non-health research should consider health is 100% correct. This is for two very fundamental reasons:

1. Interventions implemented in a health setting and/or with a health-related objective often have effects beyond health.

2. Interventions implemented in a non-health setting and/or with a non-health objective often have effects on health.

In both of the above scenarios, the unintended effect may be more important than the health effect. For example, broadening access to Medicaid in the US state of Oregon had a strong effect on financial status and wellbeing, but nugatory effects on health.[2] On the other hand, arguably the most important effect of educational interventions (especially those targeted at girls) .[3]

While most people accept the overlap in effects across 'health' and 'non-health' interventions, there is still a tendency to examine outcomes rather myopically. This is understandable because health workers exist in different cultural 'bubbles' from economists and other disciplines. Even health economists tend to take a focus on health in my experience. Health researchers more naturally collaborate with health researchers in other universities than with non-health workers in their own universities. But the barriers are breaking down. Increasingly, health and non-health outcomes are being examined to get here. For example, a recent, fascinating article in JAMA examined the financial effect of chronic disease.[4] Likewise, outcomes like ICECAP-A (ICEpop CAPability measure for Adults) [5] are also being used alongside traditional health-related quality of life. This is a very welcome trend that ARC WM is pioneering, for example, in studies of wellbeing and social care, and collaborating on evaluation of micro-finance interventions in Asia and Africa.[6]

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Detecting Data Manipulations, Large and Small

Richard Lilford, ARC WM Director

Regular News Blog readers will know that here at NIHR ARC West Midlands, we have an interest in 'targets', where an institution must exceed a performance target threshold, such as 85% frontline staff vaccinated, to earn a reward (or avoid a fine). We use analyses of data around the threshold to find out whether NHS institutions are making a general attempt to improve performance for all patients or just for those around the threshold. We look for 'manipulation', which appears in a spike of activity stimulated at the threshold level. We found evidence that there is a spike in the number of hospitals that only just make it over the flu vaccination threshold, for example, and that, as the government changes the threshold from year to year, so the spike migrates to the new threshold.[1] Clear evidence of manipulation. I was even told by an ex-chief executive that we need not have bothered with our study; *"everyone knows that this happens,"* she said.

But manipulation is everywhere. It is fascinating to gaze at tables of economic growth. But a recent article in the Economist shows that they are easily manipulated.[2] How can one tell? Well, night lighting correlates extremely well with GDP. At least it does so in countries with free political systems, as ranked by Freedom House. However, the difference between reported GDP growth and changes in lighting is non-existent in free countries, starts to open-up in partly free countries, and is a yawning gap in countries classified as 'not free'. The gap is greatest in Ethiopia, China and Rwanda, where the official figure is twice that of the objective figure. The results are generally unaffected by controlling for baseline GDP. However, dictatorships that are just below the threshold to receive international subsidies report smaller differences - another example of a threshold effect. The differences are greatest for those components of the GDP that are most malleable. It is amazing how behaviour leaves a trail in statistics - many perpetrators of financial and scientific fraud have been unmasked by tell-tale signs in the data. Individual behaviour is hard to predict, but in the aggregate we are very predictable.

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Natural Selection of Human Beings in the Great Plague

Richard Lilford, ARC WM Director

The ARC WM Director has always been interested in the great plague of the Black Death, which peaked Europe between 1347 and 1351. He has always wondered whether some people were genetically more vulnerable than others, in which case genetic selection would have taken place. He was not alone! Many have postulated such a selective process.

A recent article in Nature has confirmed this hypothesis.[1] The prevalence of a genetic marker called ERAP2 increased rapidly in English and Danish populations over the period of the plague. The researchers examined DNA from skeletons covering the critical period. ERAP2, genotype has been shown to increase the ability of macrophages to ingest *Yersinia pestis* bacteria *in vitro*.

It appears that there was a price to pay. People with the protective genotype are more at risk of certain auto-immune diseases such as Crohn's disease.

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ARC WM Quiz

Born on 28 October 1794, which British surgeon has been described as "*the fastest knife in the West End*" on account of his rapid surgeries.

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

Answer to previous quiz: In 1873 Gerhard Hansen discovered ***Mycobacterium leprae***, **the bacterial cause of leprosy.** Congratulations to Joydeepa Darlong and Alan B Cohen who were first to answer correctly.
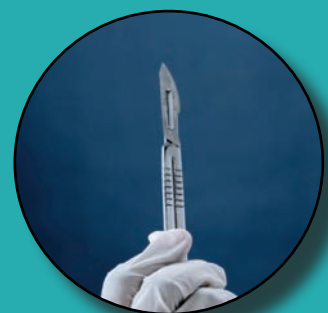
Evaluation of ePrescribing in Hospitals

Richard Lilford, ARC WM Director; Peter Chilton, Research Fellow

The long-awaited report on the NIHR Programme Grant study on the evaluation of electronic prescribing in hospitals has now been published.[1] This is the first evaluation of implementation of commercial systems. The team conducted six longitudinal case studies in hospitals that either had an embedded ePrescribing system in place or were scheduled to implement one in the future. The report shows that commercial decision support systems can reduce prescribing error by large amounts. It also shows that the extent of the improvement in prescribing depends on how the system is implemented. If nearly all of the support algorithms are implemented, these systems are highly cost-effective. The report also shows that prescribing systems can interrupt normal workflow, which could lead to new problems. This report is therefore highly relevant to the roll-out of electronic prescribing through the health service and is a guide for those who are implementing systems. An ePrescribing toolkit was also produced, which covers the entire life cycle of implementation, from conception to system optimisation.

This study built on work carried out as part of our original CLAHRC for Birmingham and Black Country, led by Jamie Coleman. Their study found that using routine data collected from an electronic prescribing system to identify doctors at risk of making serious prescribing errors had little value.[2] However, electronic decision support reduced missed doses of antibiotics in acutely sick people.[3]

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Air Pollution and Childhood Brain Development

Peter Chilton, Research Fellow

Previous research has shown that exposure to air pollution affects many facets of our health, from mental [1] to physical, including brain development during childhood. A recent study published in Environmental Pollution aimed to investigate whether there were particular periods of childhood that were more susceptible to such effects.[2]

The authors obtained MRI data from ~3,500 children aged 9-12 years, who had originally been part of a population-based birth cohort in the Netherlands. Pollution was examined using land-use regression models to estimate daily nitrogen dioxide and particulate matter levels at all participants' homes on a monthly basis, from conception to the date of the MRI scan. Temporal trends were adjusted for using a central reference site, while a number of potential confounding variables were taken into account.

Analyses found an association between exposure to pollutants and changes in the microstructure of white matter of the brain, which connects and carries nerve impulses between various areas. The authors also found an association between exposure to fine particulate matter and an increase in the volume of the putamen, an area of the brain responsible for motor function and learning processes, among other things. This association was especially pronounced during the first 2 years of a child's life. Previous research has shown associations between both altered white matter microstructure and a larger putamen with various psychiatric disorders, such as depression, anxiety and autism.

Exposure to air pollution at certain periods of life – conception, pregnancy, infancy, toddlerhood and early childhood (up to the age of 5) – were shown to be more susceptible for altered development of white matter microstructure and putamen volume. Worryingly, the levels of pollution recorded in the study were still within the current EU standards of air quality.

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Folic Acid and Suicide

Peter Chilton, Research Fellow

Taking folic acid is widely recommended during pregnancy, and it is also thought to prevent strokes and age-related hearing loss. Now a study in JAMA Psychiatry suggests it might help those with suicidal thoughts.[1] Using health records from over 850,000 US patients, the authors compared outcomes of those who had been prescribed folic acid (vitamin B9) with those who had not over a 24-month period, as well as using those who had been prescribed vitamin B12 as a negative control.

Around 80% of patients included were female, and most had been prescribed folic acid in response to a pain disorder, with almost half being prescribed 1mg per day. Analyses showed that 261 people attempted suicide or serious self-harm while being prescribed folic acid, compared to 895 such events during the months where they weren't prescribed. After adjustment, the hazard ratio for folic acid was 0.56 (95% CI 0.48-0.65). Duration-response analysis of those on 1mg/day showed that there was a 5% decrease in suicidal events per month of additional folic acid prescription. In comparison, vitamin B12 prescription had no noticeable effect (hazard ratio 1.01, 95% CI 0.80-1.27).

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Stories from History:
Dame Louisa Aldrich-Blake

Philip Simmons, ARC WM Project Administrator

Dame Louisa Brandreth Aldrich-Blake was born on the 15th August 1865, in Chingford, Essex. She attended Cheltenham Ladies' College before enrolling at the London School of Medicine for Women in 1887. She graduated in 1894 as both a Batchelor of Surgery and Batchelor of Medicine, and a year later became the first British woman to become a Master of Surgery. Fresh from qualifying she joined the New Hospital for Women and Children (founded by Elizabeth Garrett Anderson, the first female member of the British Medical Association) and the Royal Free Hospital where she was the first woman to become a surgical registrar and an anaesthetist. Throughout this time, in addition to her duties at the hospital, she continued teaching at her *alma mater* whilst pioneering new surgical methods for the treatment of both cervical and rectal cancers. In 1906 she became vice-dean of London School, then a part of the University of London, but later to become the medical school for University College London.

When the First World War broke out in 1914, she was appointed to Dean of London School. Under her tenure the number of students at the school almost doubled. Despite her already busy schedule of demanding work, she did not rest on her laurels. Using her holidays, she would travel to France and volunteer as a surgeon at the Women's Auxiliary Army Corps Hospital, based at Abbaye du Royaumont near Paris. It was here that she was given the nickname 'Madame Générale' by her patients, due to her skill and dedication as a surgeon. Through her work and the stellar work of many other female medical staff in often challenging conditions not far from the front line, they managed to persuade the initially sceptical War Office that female medical staff could do the job as well as any man. When she was not actively engaged abroad, she personally helped to recruit 48 women from the medical profession to volunteer for the Royal Army Medical Corps.

For her contributions to the field of medicine she was made a Dame Commander of the Order of the British Empire in January 1925, although she had less than a year to enjoy her title as unfortunately, she passed away in December that same year from cancer.

Her life and achievements have been honoured with a statue of her in Tavistock Square, London.

Health Determinants Research Collaborations

Coventry City Council has been awarded £5 million as part of a new NIHR programme to establish Health Determinants Research Collaborations (HDRC) around the UK. The purpose of the HDRC programme is to build a sustainable research infrastructure within local authorities, similar to those already existing in the NHS. The focus of HDRCs will be to facilitate research into the wider determinants of health and to reduce health inequalities.

Key objectives for the Coventry HDRC will be to establish research governance pathways within the City Council; provide research skills training to City Council and partner agency staff; develop pathways for deep community engagement; and embed a culture of evidence-based decision making and consideration of health inequalities in all decision-making across the City Council.

This work will be supported by partners including ARC West Midlands (Graeme Currie), the University of Warwick, Coventry University and the Institute of Health Equity (Michael Marmot), as well a number of voluntary sector organisations. The Coventry HDRC will be led by Sue Frossell, consultant in public health at the City Council, who can be contacted at sue.frossell@coventry.gov.uk.

Research Collaboration Focusing on Patient Safety

The NIHR have announced £3.5m funding for a new Patient Safety Research Collaboration (PSRC) based in the West Midlands. Co-directed by Prof Alice Turner and ARC WM Director Richard Lilford, the collaboration will be established by the University of Birmingham and University Hospitals Birmingham NHS Foundation Trust. The collaboration will conduct world-leading research to support patient safety in maternal and acute care settings.

The PSRC will bring together NHS trusts, universities, and private business to evaluate how digital tools can support clinical decision making and reduce risks for patients. It will also include a strand of work on patient preferences, since respect for individual autonomy is an important underpinning principle of safe care.

Find out more at: birmingham.ac.uk/news/2022/first-midlands-research-collaboration-to-focus-on-patient-safety.

NIHR Your Path in Research

From 31 October this year's NIHR *Your Path in Research* campaign will highlight how people can make research part of their career, with a two-week spotlight on Social Care and Public Health. Building on the momentum of this campaign, Your Path in Research will continue to be promoted until the end of the year with a focus on health research careers. For more information, visit: http://www.nihr.ac.uk/yourpath

You can also find social care and public health internships and opportunities from across all the NIHR ARCs at: arc-w.nihr.ac.uk/news/social-care-public-health-internships-opportunities/

YOUR PATH IN RESEARCH

Job Opportunity - ARC WM Dementia

A job opportunity is available for a Senior Research Fellow (0.6FTE) in a dementia research programme based at Keele University.

The NIHR, working with the Alzheimer's Society, has recently announced new funding to strengthen capacity and capability in dementia health and care research across all ARCs nationally. ARC West Midlands aims to establish a dementia research programme with a specific focus on social care. This programme of work links to existing ARC WM Research Themes (Long-Term Conditions, Social Care) and includes three inter-linked work packages, that together will identify and address broad challenges faced within the current provision of social care to those who live with dementia.

Keele University are hosting two of these work packages and are seeking to appoint a talented mid-career researcher with knowledge and experience of working within a dementia and/or social care research background.

For more information, please visit: https://findajob.dwp.gov.uk/details/10597522.

This post is advertised at 0.6FTE for two years, with a closing date of **18 November 2022**. Interviews will be held on 6 December 2022.

If you would like to discuss this position further, please do not hesitate to contact Dr Sara Muller (s.muller@keele.ac.uk).

Systematic Approach to Quality Improvement – 6 Lessons

Dr Nicola Burgess, Reader of Operations Management at the University of Warwick and part of our Organisational Science theme, has been leading a team on evaluating the partnership between the NHS and the US-based Virginia Mason Institute. Following publication of the evaluation report, Dr Burgess has produced

a summary of six key lessons for any health and care leaders who are looking to build a systematic approach to quality improvement. For more information, visit: wbs.ac.uk/news/six-key-lessons-from-the-nhs-and-the-virginia-mason-institute-partnership/.

ARCs Implementation Workshop Series - Rescheduled

A series of online workshops regarding key issues in implementation research and practice have been organised by the implementation leads across the 15 ARCs. Following the first workshop in September, the remainder have been rescheduled as follows:

• 14 Nov: Co-production in implementation.

• 12 Dec: Bringing organisation science into implementation science (*chaired by Graeme Currie, ARC WM*)

• 16 Jan: Capacity building for implementation

All workshops will take place over Zoom, running from 14:00-16:00. For more information, and to register to attend, please visit: https://arc-sl.nihr.ac.uk/node/454.

National NIHR ARC Newsletters - October 2022

The October issues of the national NIHR ARC newsletter are now available online at http://eepurl.com/h-43pH:

This issue features reports on the effectiveness of maternal mental health services; a link between devolution of health and a modest improvement in life expectancy; and an insight into how health information can be optimised for ethnic minority groups in the UK.

To subscribe to future issues, please visit: https://tinyurl.com/ARCsnewsletter.

NIHR Infrastructure Video

The NIHR have released a short video explaining their research infrastructure at: https://youtu.be/3h0OW8wusBE.

The video explains how NIHR helps and underpins healthcare research in England to reach its maximum potential.

Using Linked Health & Admin Data for Research

A joint NIHR and HDR UK webinar is being held on **2 November**, 14:00-16:00 on accessing linked data for research across a UK health data infrastructure. It will discuss the latest developments including the range of population level linked data now accessible via the HDR Innovation Gateway. For more information, please visit: hdruk.ac.uk/events/accessing-linked-data-for-research-across-a-uk-health-data-infrastructure/

EPSRC: Funding for early career researchers

The EPSRC has the following funding opportunities available:

Early career researcher collaborations for global development: Funding to initiate or develop new international partnerships with researchers overseas and to tackle the challenges faced by developing countries. [Link]

Early career researcher international collaboration grants: Funding to initiate or develop new international partnerships with researchers overseas. [Link]

Deadline for both proposals is **18 January 2023**.

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