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Clinical trials transparency at UK universities: problems and solutions

Failure to register and report clinical trials harms patients, wastes NHS resources, and slows down the development of new treatments and cures (1). For example, doctors prescribing the drug Lorcainide to patients who had suffered heart attacks inadvertently killed over 100,000 people because the results of a single clinical trial remained hidden; the UK government bought stocks of Tamiflu at a cost of £424 million before discovering that the drug's effectiveness was questionable. The best medical research is useless if its results are unreliably reported or remain inaccessible.

A study published in August 2017 by TranspariMED (2) shows that leading British universities are routinely failing to post the summary results of clinical trials onto registries. For many of these trials, the failure to post results is not only a departure from best practices, but a violation of existing European Union regulations.

Campaigners usually focus on failures of pharmaceutical companies to disclose all trial results. Companies are often suspected of intentionally hiding unflattering data on the drugs they sell, which makes them convenient – and legitimate – targets of popular outrage. However, studies consistently show that academic institutions perform even worse than the pharmaceutical industry at posting results on registries.

TranspariMED's findings suggest that academia's dismal performance is less due to greed than to ignorance and institutional indifference. But for patients, the consequences are the same: dangerous side effects of medicines may go unnoticed for a long time, potentially life-saving research goes to waste, and neither family doctors nor health officials can reliably identify the best treatment options. In short, there is no reason whatsoever to let universities off the hook.

In a nutshell, this is what TranspariMED found:

First, registry entries for clinical trials sponsored by British universities are a complete mess across the board. Out of 16 universities covered by the study, not a single one has kept its registry records complete, accurate and up to date (see Table 1). For example, the same trial is often listed on multiple registries, with each registry providing different and conflicting data on important variables such as the number of participants and outcome measures used. This undermines the entire rationale for having registries in the first place.

Second, the violation of the ethical and scientific imperatives to post summary results on trial registries is not an exception, but the norm. Due to the unreliability of data entered into registries, it is impossible to determine exactly how many completed trials are missing results. (If a trial is listed as "completed" on one registry but as "ongoing" on another, should it be counted as missing results or not?) However, comparing the total number of registry entries with the number of trials that have posted results indicates that universities post summary results for very few trials within 12 months of trial completion, which is the benchmark set by the World Health Organization.

Third, getting on top of the problem clearly has not been a priority for most universities. In response to freedom of information requests, several universities admitted that they have no idea how many of the trials they sponsored have failed to post results because they do not monitor and track their registry entries. Universities seem happy to take billions in public money to conduct medical research, but many cannot explain whether or where the results of their research can be found.

Fourth, many universities do not understand the relevant rules and regulations (see Table 2). Note that regulators and trial registries bear partial responsibility for this confusion. Their websites tend to be overly complex and written in crypto-bureaucratese, making it hard for universities and researchers to understand the rules they are expected to follow.

On the positive side, some British universities are finally starting to tackle the problem. The star performers in this regard are the University of Dundee, which has already begun to systematically clean up its registry entries and insert missing trial registry numbers into PubMed

In this issue:

Table 1: Clinical trial results posting performance of top 16 UK universities

Rank	University	# Trials total	# no results	% no results	# with results	% with results
1	**Keele**	17	12	70.6%	5	**29.4%**
2	**Dundee**	211	162	76.8%	49	**23.2%**
3	**Cambridge**	142	130	91.5%	12	**8.5%**
4	**Oxford**	590	544	92.2%	46	**7.8%**
5	**Queen Mary (QMUL)**	150	141	94.0%	9	**6.0%**
6	**University College London**	495	466	94.1%	29	**5.9%**
7	**Newcastle**	77	73	94.8%	4	**5.2%**
8	**Manchester**	136	129	94.9%	7	**5.1%**
9	**London School of H&TM**	292	281	96.2%	11	**3.8%**
10	**Imperial College London**	584	564	96.6%	20	**3.4%**
11	**Edinburgh**	278	271	97.5%	7	**2.5%**
12	**Exeter**	43	42	97.7%	1	**2.3%**
13	**Glasgow**	185	182	98.4%	3	**1.6%**
14	**Cardiff***	87	86	98.9%	1	**1.1%**
15	**King's College London**	235	233	99.1%	2	**0.9%**
16	**Swansea**	18	18	100.0%	0	**0.0%**
	TOTAL	**3,540**	**3,334**	**94.2%**	**206**	**5.8%**

** Note: Cardiff University claims that the total number of applicable trials is 37, with 36 of those missing results.*

abstracts; and the University of Aberdeen, which has pledged to carry out an audit of its existing registry entries in the wake of an earlier TranspariMED study. More universities are likely to start taking this issue seriously soon because leading research funders including the NIHR, the MRC and Wellcome Trust have recently promised to crack down on wayward grantees (3) that do not post results.

However laudable these individual initiatives are, they cannot fix a broken system. As long as universities – and pharmaceutical companies – remain free to violate ethical, scientific and regulatory rules with impunity, patients will continue to be harmed, and public resources will continue to be squandered.

After years of treating this issue as an internal family affair, the medical research community needs to face the reality that only decisive government intervention can solve the problem once and for all. A recent pilot project conducted at the University of Portsmouth has conclusively demonstrated that a national audit system for all clinical trials conducted in the UK could be set up and run at minimal cost. Using the records of Britain's 68 Research Ethics Committees (RECs), which each and every trial conducted on British soil has to pass through, such a system would use existing data to track all trials, verify whether they have been registered and properly reported, and end impunity by imposing sanctions on institutions who fail to play by the rules.

With Brexit looming on the horizon, Britain will soon have to decide how to regulate clinical trials in future. Over the coming months, TranspariMED will work with medical and political stakeholders across the UK to develop an actionable blueprint for a national audit system and push it onto the national political agenda. If you want to contribute to that discussion, I would love to hear from you.

Till Bruckner, TranspariMED
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Table 2: Misconceptions about requirements for clinical trial posting

MYTH	FACT
We only have to register CTIMPs or Phase II–IV trials.	All clinical trials have to be registered. UK regulations, the Declaration of Helsinki and the International Committee of Medical Journal Editors (ICMJE) all clearly state this.
We only have to post summary results for some types of trials (such as CTIMPs), or for those conducted from a certain date onwards.	Results sharing is a universal ethical obligation according to the Declaration of Helsinki, and a universal scientific obligation according to the WHO, irrespective of national regulations.
We are not responsible for posting trial results, researchers are. For example, when the lead researcher of the trial moves on, our responsibility ends.	EU regulations state that the trial sponsor (i.e., the university) is responsible for posting results.
If our researchers fail to keep registry entries up to date, it is not our fault.	EU and US regulations state that the trial sponsor (university) is responsible for regularly updating registry entries.
We can wait until a journal has published the paper before we post summary results onto registries.	WHO guidelines clearly state that 12 months is the maximum time limit for posting results, irrespective of academic publication status.
We are only responsible for trials we formally sponsor.	Universities are responsible for ensuring that their employees adhere to universal ethical and scientific obligations, and to national laws.
This is not a priority. Getting our registry entries in order can wait.	Major funders will reconsider funding to irresponsible researchers. TranspariMED will regularly publish universities' performance rankings.

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News

Fearless talk at this year's AGM

This year's HealthWatch Award winner was Dr Deborah Cohen, the *BMJ's* fearless Investigations Editor. She kept her audience spellbound for almost an hour with shocking tales of what happened when she asked awkward and unwelcome questions about drugs, medical devices, fertility aids and sports drinks. The AGM took place on 17 October, at the Medical Society of London. Full reports are being prepared for the Winter issue of the HealthWatch Newsletter.

Our submission to House of Commons inquiry into Research Integrity is now online

HealthWatch recently responded to the Government's consultation on research integrity, as joint signatory to a proposal to address the issue of incomplete and inaccurate reporting of clinical trials. The proposal, drafted by Till Bruckner of TranspariMed and co-signed by Universities Allied for Essential Medicines UK, TranspariMED, and Dr Simon Kolstoe, calls for a national clinical trial audit system that would strengthen research integrity by monitoring the registration, summary results posting and academic publication of every trial conducted in the UK.

The inquiry is currently hearing oral evidence. You can follow the progress of the inquiry at https://www.parliament.uk/business/committees/committees-a-z/commons-select/science-and-technology-committee/inquiries/parliament-2017/research-integrity-17-19/ and our proposal is available online at http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/science-and-technology-committee/research-integrity/written/70815.pdf

Prizes for Skeptics

Congratulations to Edzard Ernst, for winning this year's Ockham Award in the Editors' Choice category. The Ockham awards are presented annually by Skeptic Magazine. Professor Ernst, emeritus professor of complementary medicine at the Peninsula School of Medicine, University of Exeter was commended for his research into alternative and complementary therapies, and his blog at http://edzardernst.com/. Another worthy Ockham winner was fellow blogger Crispian Jago for his funny, dark diary of life (so far) with kidney cancer, Always Look on the Bright Side of Death (http://rationalcancer.blogspot.co.uk/). The awards were presented at QEDcon, a science and skepticism convention held in Manchester on 14–15 October. https://www.skeptic.org.uk/ockham-awards-2017/vote/

Patience with homeopathy is running out all over the world

NHS England is currently digesting the responses to its recent consultation into items which GPs should not routinely prescribe in primary care. As they ponder the question of homeopathy, support for the discredited therapy continues to collapse in other parts of the world. The Russian Academy of Sciences recently declared that it "has no scientific basis" and, further, that "Homeopathy is not innocuous: patients spend heavily on non-performing drugs and neglect means of treatment with proven effectiveness". The Academy's Commission against Pseudoscience and Falsification of Scientific Research urged the media to present homeopathy as a pseudoscience on a par with magic, healing, and psychic practices (Independent, 17 February 2017, http://www.independent.co.uk/news/world/europe/russia-academy-of-sciences-homeopathy-treaments-pseudoscience-does-not-work-par-magic-a7566406.html).

Now television channels in India have been instructed to stop broadcasting misleading ads for ayurvedic, siddha, unani and homeopathic (AYUSH) drugs. A notice stamped and signed from the Government of India Ministry of Information & Broadcasting warns of the potential health risks from treatment by the "self-proclaimed Doctors, Gurus, and Vaidhs offering miraculous solution of all health problems". https://www.homeowatch.org/reg/india/mib_2017.pdf

Make room on your bookshelf

No Way to Treat a Friend—Lifting the Lid on Complementary and Alternative Veterinary Medicine by Niall Taylor and Alex Gough, published by 5m books for £14.95, exposes the flawed beliefs around the use of alternative remedies in animals. explains how they may appear to respond to treatment even when it is ineffective; and examines homeopathy, acupuncture, raw diets and the anti-vaccination lobby. http://www.5mbooks.com/no-way-to-treat-a-friend-lifting-the-lid-on-complementary-and-alternative-veterinary-medicine.html

Treatments

Electronic fetal monitoring in labour and cord clamping at birth: *A comparison of physiology, medical logic and evidence based medicine to reduce prenatal mortality and morbidity*

At first sight there is no obvious relationship between continuous electronic fetal monitoring (EFM) in labour and delayed cord clamping at birth. However both, based on physiological logic, could affect risk of death and morbidity in newborns. The whole purpose of EFM in labour is to identify intrapartum hypoxia (dangerously low oxygen levels) and then to deliver the baby to the care of the neonatal team before any significant brain injury has occurred. Early cord clamping (ECC), originally part of routine third stage management of labour (1), has permitted the rapid transfer of the infant away from the mother for resuscitation when required. In an ideal world recognition of early fetal distress by EFM would result in delivery *before* the onset of asphyxia with little or no neonatal resuscitation being necessary.

However, there is very limited evidence for any benefit of EFM in labour, and the research continues (2,3). A reduction in neonatal seizures is the only benefit shown so far. Early cord clamping was introduced without any evidence and now there is evidence *that it is harmful* (4). The long-standing practice of ECC and the continued practice of resuscitation away from the mother is slowing its removal from practice (5,6). To simplify this discussion we will only include babies born full-term.

EFM

Labour is known to be one of the commonest times when a fetus risks hypoxia (7). The fetal heart rate is well recognised to be affected by hypoxia (8). The modern cardiotocograph, or CTG, can measure and document the foetal heart rate during labour. Although non-invasive, this monitoring cannot be considered completely benign and may be one of the underlying causes of the dramatic rise in the caesarean section rate over the last 30 years (3,9). Interpretations of CTG data made during the birth process, when considered in retrospect, are often considered substandard (10).

Early cord clamping

While the monitoring may be only minimally invasive, the fully invasive nature of early cord clamping has only recently been fully recognised. It has been shown to have no role in reducing the risk of post partum hemorrhage and there is theoretical and randomized controlled trial evidence of considerable harm caused by early clamping (11).

Transition of fetal to neonatal circulation

The patterns of fetal blood circulation and the circulatory system in the neonate are well understood. The process of transition between the two is less well understood but recent computer simulation and lamb studies confirm that there are dramatic changes in the baby's circulation when the cord is clamped early before the pulmonary circulation is established (12). Early clamping results in a marked increase in afterload of the heart followed by a marked fall in the heart's preload. In some situations it has been proposed that early cord clamping could result in a marked fall in circulation of blood to the brain and hypoxia resulting in an acute neurologic emergency. As a result a few babies will develop permanent brain damage (13). Many of these babies go on to develop cerebral palsy or die. Randomised controlled trials show early cord clamping leads to neonatal anaemia and iron deficiency (3). Other harms are emerging if there is intrapartum cord compression and early cord clamping results in hypovolaemia – severely reduced blood volume (14).

In birth asphyxia, ventilation is a priority (5). Current practice is for the newborn baby to be moved to a resuscitation machine remote from the mother. However it is possible for the cord to remain intact with motherside neonatal resuscitation (15).

The admirable initiative by the RCOG of the Each Baby Counts study has concentrated on term intrapartum care (16). It concluded that staff failed to interpret the cardiotocograph data accurately enough to prevent death and severe morbidity in the neonate. To correct this, the study authors recommended that all staff tasked with CTG interpretation must have documented evidence of annual training. CTG interpretation was *the only specific factor* identified which may have prevented their death or brain injury.

Of course, those assessing CTG monitoring data do so in the comfort of an armchair and with the knowledge of the poor outcome. This finding is not new and it has been thought that an expert computer analysis of the CTG would result in improved interpretation and outcomes. This approach has not, however, shown an improved outcome (17). The intervention of early cord clamping was never considered in the Each Baby Counts study and, in fact, ECC would have been the norm.

There is indisputable evidence that early cord clamping results in a variable degree of hypovolaemia in the newborn baby (18). As with any blood loss, the lower end of the spectrum is tolerated. It is only at the upper extreme that severe problems will occur. This can be volume reductions of as much as 214ml (18).

No matter how good the cardiotocograph interpretation and no matter how appropriate and timely the delivery of the baby, any subsequent maltreatment of the baby may

drown out any benefits of the CTG. If the maltreatment inflicts a very different form of injury it may be obvious. However if the maltreatment results in a similar insult of hypoxia and ischaemia it will be impossible to identify which of the procedures was the cause of the harm.

Cord compression leads to compression of the cord vein greater than in the cord arteries, and a transfer of blood volume from the baby into the placental compartment. The reduced flow of oxygenated blood in the cord vein leads to typical changes in the pattern of the fetal heart. Some cord compression in labour is common. When these babies are delivered there is already a concern, from the CTG, that there may have been some intrapartum hypoxia, and also a concern that there may be a need for neonatal resuscitation. Thus early cord clamping is likely to be common. Early cord clamping in these babies permanently traps the blood in the placenta. But if the cord is left intact after the baby is born and the cord compression has been relieved, there is an opportunity for a rapid return of the blood in the placenta into the neonate. This oxygenated blood may be all that is required to allow the baby to recover on its own. If this recovery is not apparent, resuscitation with ventilation can then be carried out at the side of the mother with an intact cord.

The value of electronic fetal monitoring in labour remains unproven but there is good evidence for the harmful intervention of early cord clamping. Until this is stopped we will never know how many of these baby deaths are truly preventable. The timing of cord clamping must be documented in every birth and the NICE guideline followed for timing.

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Nutrition

The Pioppi Diet

***The Pioppi Diet, A 21-Day Lifestyle Plan*, by Dr Aseem Malhotra and Donal O'Neill comes with a promise "Lose weight, feel great and drastically reduce your risk of Type 2 diabetes and heart disease." The plan is based on the example of people living in the village of Pioppi in Southern Italy. The fact that the 200 or so citizens of Pioppi live very long and healthy lives makes it worthwhile studying their lifestyle, including their traditional peasant-style Mediterranean diet. *The Pioppi Diet* extols the benefits of the daily physical activity associated with their rural life, regular sleeping patterns, lack of stress and their excellent social interactions, but diet dominates the discussion.**

The health benefits of Mediterranean diets have been well studied and published. Indeed, researchers have established a Mediterranean 'Diet Index' using various scoring systems for the dietary factors that contribute to these healthy diets (1, 2). The people of Pioppi score highly on any version of this index, with their daily meals consisting of lots of vegetables, legumes, grains, fruit, fish, olive oil and nuts with modest consumption of cheese, yoghurt, coffee and wine, and low intake of meat. Very little sugar or highly processed foods are consumed and dessert is an occasional treat. Like all Mediterranean diets, the diet in Pioppi is low in saturated fat.

It's strange, then, that the version of the Pioppi diet espoused in this book varies from this long-standing dietary pattern. For example, bread and grain foods, always part of the meal table in Pioppi, are forbidden while coconut fat and various fermented products that are not part of the Pioppi diet have been added to the authors' recommendations, along with a daily treat of 30g of dark chocolate. And would the people of Pioppi ever make a pizza with the usual yeasted dough base changed to one made of cauliflower, as suggested in this book?

The variations fit the authors' well-known enthusiasm for low carbohydrate/high fat diets with no restrictions on saturated fat. However, the changes they make are foreign to the actual diet followed for centuries by the residents of Pioppi.

Pioppi was also the chosen home of Dr Ancel Keys and his wife Margaret for decades during their long lives. They loved the simple lifestyle and the diet that fitted so well with what Keys had promoted. In the 1950s and 60s, Keys and co-workers had carefully documented the effects of particular saturated fatty acids on blood cholesterol. They then conducted the Seven Countries study. From the 16 population groups in this extensive study, the evidence for cardiovascular disease strongly favoured the benefits of traditional Mediterranean or Japanese diets – both low in saturated fat (3).

Choosing Keys' much-loved home for the title of this book is strange when Malhotra has been a prominent critic of Keys' work, claiming his emphasis on reducing saturated fat intake led to a huge increase in consumption of the real culprit – sugar (4). Indeed Malhotra claims that Keys' studies influenced dietary guidelines which he holds responsible for the massive increase in obesity and type 2 diabetes. In fact, few people follow dietary guidelines so it's a bit rich to blame them for anything. Also, in their 1959 book *Eat Well and Stay Well*, one of Keys' and his wife, Margaret's, guiding principles was to reduce intake of sugar (5).

Contrary to the claims made by critics, neither Keys nor dietary guidelines have ever recommended more sugar or processed foods in which the fat is replaced by refined carbohydrates. The Australian guidelines, for example, have always recommended limiting sugar and choosing wholegrains in preference to refined grains.

Dietary guidelines did originally recommend reducing saturated fat by recommending diets low in all fat. More recently, however, guidelines throughout the world have recommended swapping foods high in saturated fats for those containing unsaturated fats, found in olive and other liquid oils, nuts, seeds, legumes, fish and avocadoes. Most guidelines have also always recommended limiting sugar.

In assigning blame for increased obesity, it is the lure of cheap convenient junk foods, promoted by processed and fast food companies, that has led to increased total calorie consumption. The decrease in everyday physical activity has not helped.

The world's publicity machine went into overdrive when a meta analysis reported a lack of correlation between the amount of saturated fat reported in dietary surveys and cardiovascular disease and total mortality (6). Malhotra supported this conclusion, although it found no positive benefits for saturated fat intake and a careful analysis of the report has since shown significant errors (7). What replaces *saturated fat is important. If sugar and refined starches are chosen as replacements, there is no benefit (8).* However, there is good evidence of cardiovascular benefits if saturated fat is replaced with polyunsaturated fat (8) or with wholegrains (9) – both of which dovetail with the Mediterranean diet.

The questions I'd attach to dietary advice in this book include:

- How valid is it to make claims based on a doctored version of the actual diet of the people of Pioppi? And why deviate from the proven benefits of the traditional diet that is still followed?
- Why 21 days? The people of Pioppi follow their diet for life, whereas a short-term trial aligns more with fad diets.
- Why add coconut? There is virtually no coconut in the Pioppi or any traditional Mediterranean diet. (Incidentally, like many who promote a high fat/low carb diet, Malhotra wrongly categorises the chief fatty acid in coconut, lauric acid, as being digested and absorbed like fatty acids with 6, 8 or 10 carbons in their chain.)
- Why include chocolate daily? The people of Pioppi, like others who follow traditional diets, keep sweets and rich foods for special occasions.

- Fermented foods have many nutritional virtues, but the usual diet in Pioppi relies on the proven benefits of fermented dairy products like cheese and yoghurt.

If people follow this version of the Pioppi diet, they may well lose weight – at least initially. There's nothing magic about that. No nutritionist would quibble with minimising processed foods but weight loss is likely due to the reduction in total energy intake compared with usual consumption patterns.

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Meeting report

NHS England's public consultation event: dropping homoeopathic remedies from the medicines list

On 5 September 2017 NHS England held a public consultation event about a list of medicines they are considering dropping from the list prescribable list. I went on behalf of HealthWatch.

The medicines fell into three groups: things that don't work, those that can be bought cheaply over the counter, and those that are potentially harmful. And some travel vaccines.

Three people were in charge: Neil Churchill, director of patient experience; Bruce Warner, deputy chief pharmaceutical officer; and Graham Jackson from NHS central commissioning.

Though it was NHS England only, they said that the final recommendations would probably be followed in other parts of the UK.

About 50–60 people attended and we were pre-allocated to one of eight tables. I found myself with two young men from a prostate cancer charity, who were there to defend Tadalafil, a Viagra-type medicine; a vociferous patient who took prescribed homeopathic remedies for bronchiectasis, and her friend, head of the League of Friends of what was once called the Homeopathic Hospital; and Simon Singh, who needs no introduction.

Someone from NHS England sat at each table, taking notes and trying to keep the conversation on course. While we talked, the commissioning group doctor visited our table, and what he said was most helpful. He explained that Tadalafil was relatively ineffective and significantly dangerous; the two prostate cancer charity men clearly hadn't known this, and took the information on board. It is a reflection of how patient support groups are dependent on drug company money, and don't realise when they are being had.

He also said that current travel vaccines policy was currently a mess, irrational and with regional variations. They want to rationalize it, offering free NHS vaccination against only those diseases that would cause a public health problem if brought back into the UK.

The lady with bronchiectasis is a patient at the Brompton and sees a homeopathic doctor – surely not there? She said her prescriber tries out different remedies, which belies the idea that homeopathic remedies are specific. And that breathing exercises don't work for her.

I too have bronchiectasis. It's a condition, as I understand it, where the airways are dilated and are missing many of the cilia that waft muck and mucus up and out. So a sump of M&M collects, an open invitation to pathogenic bacteria. The treatment is breathing exercises, huffing so that the muck is pushed up far enough for it to be coughed out. The exercises aren't easy and I find I have to work at them, but they have a logical base, and they work.

Simon was marvellous. He told the bronchiectasis lady that he'd talk to her afterwards, and did. I sat listening while he pointed out that once upon a time, many people swore by bloodletting, but that didn't mean it worked. And a huge number of Asian Brits swear by astrology and would use it if it the NHS offered it; and I was impressed by his humour and friendliness. The homeopaths knew who he was, a secular equivalent of the antichrist, and probably marvelled at what a nice person he was, though wrongheaded, of course.

As I left, a number of people asked me what side I represented. Evidence, I said. You? Homeopathy, came the answer.

Caroline Richmond

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Letter to the editor

NHS national list of "low value" drugs: is this no more than window dressing?

The BMJ recently published a news item titled "NHS will publish national list of 'low value' drugs to curb GPs' prescribing costs" (1). I'm not sure that this is good news and in my opinion the journal may have failed to adequately comment on the news.

First, the title seemed to be shaming GPs for prescribing. Happily, NHS England claimed its plans were "drawn up with family doctors and pharmacists" (2). Family doctors are at the front line, with the most difficult job of all, and scapegoating is useless. A root-cause analysis should investigate why regulatory agencies are like leaky sieves granting marketing authorizations for products with unproven health benefit and reimbursing their costs. Because who is responsible for this problem: the family doctor or the experts of the scientific taskforces of the regulatory agencies?

Second, the NHS national list will be restricted to products intended "for minor self-limiting conditions" focusing on "homeopathy … cough mixtures and cold treatments, eye drops, laxatives …". To me, it seems a smokescreen.

NHS Wirral Clinical Commissioning Group (CCG) ceased funding for homeopathy in 2016 and presently very few CCGs are still commissioning it. The national list will only be an acknowledgement of this fact. Moreover, any discussion about homeopathy surely belongs in the category of stopping funding insanity rather than any sensible discussion about saving costs. This is my opinion, even as a Frenchman – I am well aware that the turnover of the French company Boiron, the world leader in manufacture of homeopathic products, exceeds €610 million, because their products are reimbursed by our mandatory healthcare scheme.

The NHS should not ignore Prescrire's "Choosing Wisely" initiative (3). The French independent drug bulletin publishes yearly a list of "drugs to avoid": drugs with adverse effects that outweigh their benefits or those that have been superseded by others with a better harm-benefit balance. There are now 91 "drugs to avoid" (4), most marketed worldwide with almost no action from regulatory agencies! Prescrire also advises clinicians how to choose treatments, ranking them on a scale of 1 to 7, from "bravo" to "not acceptable" (5).

Among a too-long list of scandals, strontium ranelate is close to the top. It would be too easy to claim that it should have not be granted a marketing authorization in 2004. Indeed, errors can occur. The worst is that despite robust evidence, as early as 2006, which showed that strontium ranelate increased the risk of myocardial infarction and congestive heart failure, there has been no action from the European Medicines Agency (6). The year previously, in 2005, Prescrire had warned against its use (7). To this day there has been no revocation of the marketing authorization by the Agency, only a "cessation of supply" by the company in 2017 (8).

Regulatory agencies have a difficult task. But they are like a car with only two speeds: too fast and too slow. They are too fast to approve and too slow to withdraw (9). In the face of what is already an incontinence of marketing authorizations (10) the European agency has recently increased the speed of approval even further (11). Meanwhile, market withdrawal is unreasonably delayed, even in the case of drug-related deaths (12), and drug withdrawals for commercial or financial reasons are more frequent than those prompted by harms or inefficacy (13).

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Last word

Yet another scare story about breast cancer risk

In my long career as a breast cancer clinician I have been repeatedly plagued by news stories about risk factors for breast cancer that result in panic amongst the female population. These have included underwired bras, deodorants, long haul flying and abortion; to mention just a few. This week's scaremongering relates to hair dyes (1).

In every case the flaw in the reasoning is the same, and at this point I will use upper case letters to indicate that I'm shouting: ASSOCIATION DOES NOT INDICATE CAUSALITY.

Let me illustrate that with both a silly example and a more serious example.

a) Sitting on leather chairs causes obesity

Therefore, those at risk of obesity should avoid contact between buttocks and leather because of the toxic properties of tannins in the leather impacting on metabolism.

I hope the fallacy is self-evident.

b) The more television you watch the greater the risk of breast cancer

This is true but the rays from your TV aren't the cause. In this example, there are many "confounding variables". At a global level the ownership of televisions and the leisure to watch box sets on NETFLIX is directly correlated with the GDP of the country you live in.

Women in low-income countries, such as in Sub-Saharan Africa or Bangladesh, have a shorter life expectancy than those in countries with high incomes. Such women also experience a late menarche and an early menopause. In contrast, women in countries with a high GDP eat a "western diet", can turn a tap to get clean water rather than walking four miles to the nearest well, enjoy the leisure to watch TV, and are at increased risk of obesity. Apart from family history, the three commonest risk factors for breast cancer are age, length of time between menarche and menopause and post-menopausal obesity.

The last observation is explained by the fact that after the menopause oestrogens are synthesized within adipose tissue (how that happens is not relevant at this point).

From these examples, you will see that the science of epidemiology is not a case of simple cause and effect. Coming back to hair dye and risk of cancer, there are no end of potential confounding factors. My best guess is that hair colour relies on the function of the melanocytes in the skin. Melanocytes should be considered hormone responsive cells. Premature greying of the hair might be linked to subtle imbalances of the endocrine (hormone) system (2,3).

Whatever the underlying cause women should be reassured that the additional risk is very small. A 15% increase sounds alarming, but translating this into absolute numbers presents a different picture. The risk of the average woman developing breast cancer in the age range 50–75, is 2 per 1,000 per year, or 20 in a decade. Fifteen per cent of 20 equals 3, or in other words an extra three women will be diagnosed with breast cancer amongst a thousand women over a decade. Of these most will die of "natural causes" because of advances in the treatment of the disease. It is said that worrying will give you grey hairs; stop worrying about dyeing and live your life to the full.

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