this week

NEW MONEY FOR EXTENDED GP HOURS page 2 • **MEDICAL PHILANTHROPISTS** page 3

OLI SCARFF/GETTY IMAGES

Trusts move towards new contract

Trusts in England are preparing to transfer trainees onto the new junior doctors' contract as BMA leaders have vowed that they will continue to oppose its imposition.

On Saturday 24 September the BMA said that it was planning actions to resist a new contract for junior doctors in England after the union suspended five day strike action planned for October, November, and December.

However, trusts have said that they are preparing to move obstetrics trainees onto the new contract from October, and they have already been using rotas that are compliant with the new contract.

Andrew Foster, chief executive of Wrightington, Wigan, and Leigh NHS Foundation Trust, told *The BMJ* that 179 doctors in training at his trust were now working on rotas compliant with the new contract. "All of our rotas have been redesigned to comply with the new contract terms and conditions," Foster said. He added that third year specialty trainees in obstetrics "will transfer to the new terms and conditions as per the national implementation schedule."

Catherine Free, deputy medical director at University Hospitals of Leicester NHS Trust, said that the first trainees would transfer to the new contract in December. "A review of the existing rota templates has shown that 60% of the junior doctor rota templates will need to be revised in line with the new rota rules. [The] majority will only require minor modifications," she said.

Trainees at Lancashire Care Trust would not be moving onto the new contract until later in the year, while those at the University Hospitals Bristol NHS Foundation Trust would not be transferring until February 2017, trusts told *The BMJ*.

Last Saturday Ellen McCourt was re-elected as chair of the BMA Junior Doctors Committee (JDC). In an email to members, McCourt said that although strike action was suspended "the JDC still opposes the implementation of the contract." She said that the JDC would be "planning other actions" to resist the imposition and that the BMA "will be coming to you in the next few days to discuss and explain these actions to you."

The ruling on whether Jeremy Hunt's decision to impose the junior doctor contract was lawful was due to be made on 28 September, after *The BMJ* went to press.

Abi Rimmer BMJ Careers, Susan Mayor London

Cite this as: *BMJ* 2016;354:i5267

See CAREERS, p 6

The new junior contract will officially begin its roll out on 5 October

LATEST ONLINE

- Workload pressures are leading to unsafe hospital discharges, say MPs
- US doctors recommend continuous glucose monitoring for patients with type 1 diabetes
- GMC closes inquiry into troubled Aberdeen hospital

SEVEN DAYS IN

CCGs will get £6 a patient to extend hours

Every clinical commissioning group (CCG) in England will be given recurrent funding of at least £6 per head of population to allow GP surgeries to extend their opening hours, NHS leaders have announced.

CCGs will be required to commission at least an extra 1.5 hours of evening appointments after 6 30 pm on weekdays but will have the flexibility to offer Saturday and Sunday appointments according to local need.

The BMA said that it was pleased that NHS England had accepted that it was "a nonsense" to force GPs to open from 8 am to 8 pm on Saturdays and Sundays.

The funding will initially be released during 2016-17 in areas of England that have been piloting extended hours and expanded to the rest of the country in 2017-18, with every CCG set to receive the additional money by April 2019. The total investment will reach £258m in 2018-19.

Richard Vautrey (left), deputy chair of the BMA's General Practitioners Committee, welcomed the recurrent funding available for extended opening but added that £6 a head was "much much less" than some pilot sites had been operating with.

He said, "Those sites will have to cut their cloth accordingly and either reduce the number of appointments or use a greater degree of skill mix to provide that extended service."

Gareth Iacobucci, *The BMJ* Cite this as: *BMJ* 2016;354:i5203

Cardiac arrest

Europe-wide cardiac arrest phone number is urged

The European Resuscitation Council, the European Board of Anaesthesiology, and the European Society of Anaesthesiology urged hospitals in Europe to use the same internal telephone number—2222—to summon help when a patient has a cardiac arrest. A study in Denmark showed that 74 hospitals used 41 different numbers and that 50.5% of staff did not remember their hospital's own number.

Obstetrics

Nausea is linked to low risk of pregnancy loss

Nausea in pregnancy is associated with a 50% reduction in risk for pregnancy loss, and nausea with vomiting is linked to a 75% reduction, a prospective study in *JAMA Internal Medicine* found. Commentators said that, while nausea and vomiting in pregnancy "may provide reassurance to some women, they should not be discouraged from seeking treatment for a condition that can have a considerable negative effect on their quality of life." (doi:10.1136/bmj.i5232)

Temperature is not always checked in premature babies

Only 93% of premature babies had their temperature measured as recommended in the first hour after birth, and more than a quarter were below the recommended range of 36.5°C to 37.5°C, the UK national neonatal audit found. Sam Oddie, clinical lead for the programme, said that the finding was "very concerning. If not monitored closely, low admission temperature can lead to hypothermia and severe illness, so getting this right is essential." (doi:10.1136/bmj.i5219).

GMC rulings

GP is struck off after abortion drug "sting"

Majeed Ridha, 67, a privately practising GP, was struck off the UK medical register after supplying misoprostol to an undercover reporter. Ridha was consulted in London's Cumberland Hotel in 2012 by a man who said that he wanted to give the drug to a woman who "doesn't want to go to an abortion clinic." Ridha arranged for a pharmacist to give misoprostol to the man and charged him £250, unaware that he was the undercover reporter Mazher Mahmood, popularly known as the "fake sheikh." (doi:10.1136/bmj.i5181)

Cancer

Red flag symptoms are missed in bowel cancer

Nearly one in five patients who have bowel cancer diagnosed after presenting as an emergency had at least one "red flag" symptom in the year preceding diagnosis, a study in the *British Journal of Cancer* found. More than a third (35%) of 1029 people with colon cancer diagnosed in England during 2005-06 and

15% of 577 people with rectal cancer got their diagnosis on emergency presentation. But 17.5% of those with colon cancer and 23% with rectal cancer had had at least one red flag symptom—including rectal bleeding and abdominal pain—recorded in their notes in the previous year. Cristina Renzi, lead researcher and Cancer Research UK scientist at University College London, said that the study highlighted "the need to support GPs and give them the tools to diagnose and refer patients promptly when they feel it's necessary."

Elderly care

Call for action on older people's needs

The UK's ageing population is let down by an inadequate and fragmented health and social care system, a new BMA report warned. It called for action to tackle social

MEDICINE

isolation in older people by focusing on "social prescribing"—connecting them to non-medical and community support services. It also urged better treatments for mental health conditions, greater involvement of carers with adequate information and advice, and societal change to recognise older people's contributions.

Wearable technology didn't help people keep weight off

NHS

Thousands more NHS operations are cancelled

Nearly 42 000 operations were cancelled in 2015-16 one to three days before patients were admitted to hospital, but these were not recorded in official figures, a BBC investigation found. NHS England requires hospitals to inform it only when an operation is cancelled on the day or the day before it is scheduled. Some 74 806 operations were cancelled in 2015-16—the highest figure in 15 years.

Clear plan for digital NHS is needed

The government and NHS leaders must set out a clear and compelling plan for expanding the use of digital technology, a King's Fund report said. Digital technology can transform how patients engage with services and can improve efficiency and care coordination, the fund said, but it warned that expectations may be set too high amid financial and operational pressures. All levels of staff, particularly clinicians, should be involved in designing and rolling out new technology for the plan to succeed, said the report. (doi:10.1136/bmj.i5185)

Research news

Fitness device does not maintain weight loss

Participants in a randomised weight loss study who used a wearable fitness device to monitor physical activity lost less weight over two years than those who self monitored their diet and activity using a website, a study in *JAMA* found. John Jakicic, lead author, said that some wearers may give up on restricting calories because the device tells them how far short of their exercise goals they are—breeding fatalism—while others may justify overeating because the devices show how many calories they have burnt off through exercise. (doi:10.1136/bmj.i5204)

Farm childhood may protect against allergy

People who grew up on a farm show half the risk of atopic asthma and rhinitis in adulthood than those who had an inner city childhood, a study of 14 European countries found. But people who spent their first few years in a village, town, or suburb showed no reduction in adult allergic conditions. The researchers said that "the consistency of the findings across multi-country settings suggests that farming effects may be due to biological mechanisms rather than socio-cultural effects that would differ between countries." (doi:10.1136/bmj.i5223)

Cite this as: *BMJ* 2016;354:i5246

MMR UPTAKE

Measles, mumps, and rubella (MMR) vaccination rates fell to **91.9%** in 2015-16, down from **92.3%** in 2014-15 and **92.7%** in 2013-14

SIXTY SECONDS ON . . . MEDICAL PHILANTHROPISTS

NOT BILL GATES AGAIN?

No, the Microsoft founder and scourge of infectious diseases, Bill Gates, has a rival to the title of saviour of the world. Mark Zuckerberg, the man behind Facebook, and his wife, Priscilla Chan, have pledged £2.3bn over the next decade to "cure, manage, and prevent all diseases within our children's lifetime."

ALL DISEASES? IS THAT POSSIBLE?

Zuckerberg says that scientists have told him that his aim is not only possible but "will be one of the most important things that our generation leaves for the next generation."

IT'S A LOT OF MONEY, £2.3BN

Not really. The Wellcome Trust and Cancer Research UK both spent about a quarter of that in just one year. In 2015 Wellcome spent £613.5m on scientific activities, while in 2015-16 Cancer Research UK spent £658m.

IT'S A LOVELY THING TO DO

Yes, but some people have questioned the rise in "philanthrocapitalists" (the term coined by the *Economist* to describe donors who use the power of the market in their giving), asking whether their focus on pet projects is skewing research funding. A study by Fiona Murray, professor of entrepreneurship at Massachusetts Institute of Technology, found that 30% of the research funding of leading universities in the US came from private funders. In a book about the Gates Foundation the Essex University sociologist Linsey McGoey argued that, although it has undoubtedly done a lot of good, any organisation that spends more on global health research than a nation such as Germany should be more accountable.

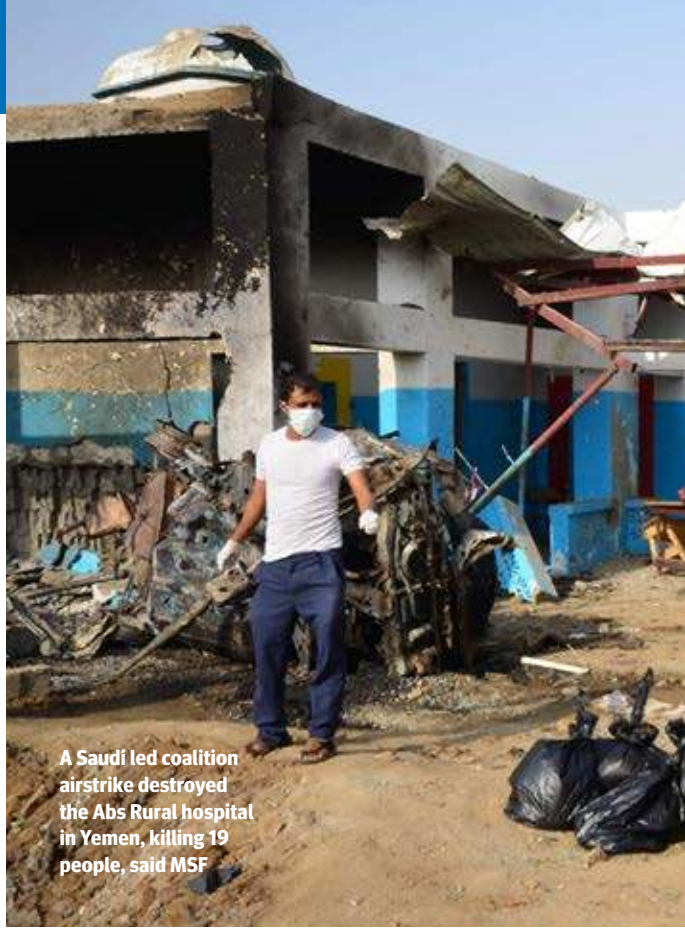
WHAT DO OTHER RESEARCHERS THINK?

It has been welcomed all round. Jeremy Farrar, director of the Wellcome Trust, applauded Zuckerberg's largesse while pointing out that his institute will spend £5bn over the next five years on health research. Paul Reiter, recently retired professor of medical entomology at the Pasteur Institute, said that accusations that Gates had too much control over research was partly true but also "part sour grapes."

Anne Gulland, London

Cite this as: *BMJ* 2016;354:i5192

UK must stop arms sales to Saudi Arabia, urge doctors



A Saudi led coalition airstrike destroyed the Abs Rural hospital in Yemen, killing 19 people, said MSF

The charity Medact has called on the UK international trade secretary, Liam Fox, to suspend arms sales to Saudi Arabia to prevent further bombing of healthcare facilities in the conflict in Yemen. Fox, who studied medicine in Glasgow and worked as a GP in Buckinghamshire before entering politics, is now responsible for licensing arms sales.

Campaigners from Medact, a charity for health professionals focused on global health improvement, and other doctors and health professionals have appealed to Fox as a doctor to think of the health of Yemeni people, the brutal attacks on clinicians, and his duty to "first do no harm." They cited evidence that British arms were being used to bomb hospitals and other civilian buildings in Yemen by the Saudi led coalition, enabling a growing "health catastrophe."

The air campaign in Yemen began in March 2015. The parliamentary International Development Committee has emphasised that the UK government sold more than £3bn worth of weapons to the Saudis between April and December in 2015.

Last week an open letter by four of Medact's campaigners, signed by more than 200 leading doctors and health professionals, urged an immediate cessation of these sales. The letter said that in the 18 months since the outbreak of armed conflict in Yemen 2.4 million people have been forced to flee their homes and 22 million have needed humanitarian support.

Now Medact is asking doctors more widely to tweet to @LiamFoxMP or email him at ione.douglas@parliament.co.uk to add their voices to the campaign.

David McCoy, director of Medact and director of global health teaching at Queen Mary, University of London, said that there were parallels with the Syrian war. He told *The BMJ*, "The mess in Syria will not be solved by Britain pointing fingers at Russia while we sell arms to Saudi and turn a blind eye to the atrocities in Yemen. The health community really should be speaking out."

The open letter was followed by an emotive personal plea to Fox from the joint coordinator of Medact's arms and militarisation group, the trainee GP Sarah Alhulail. She described how in August a Médecins Sans Frontières hospital in northwest Yemen was

"As health professionals, we have a duty to speak out against all causes of ill health in Yemen"

The parliamentary International Development Committee has emphasised that the UK government sold more than £3bn worth of weapons to the Saudis between April and December 2015

Novel itch remedy wins Ig Nobel medicine prize

Thomas Twaites said that his project was about taking a holiday from being human by becoming a goat

Neurologists from the University of Lübeck, Germany, have won the 2016 Ig Nobel prize for medicine for showing that if you deceive the brain you can relieve an itch on the right side of a limb by scratching the equivalent spot on the left side.

Andreas Sprenger, one of the prize winning researchers, told *The BMJ* that participants were tricked with mirrors or videos to think that the real itch was being scratched when actually a spot on the opposite arm was. The relief worked only when the participant was deceived.

The method might be useful when people scratch at a severe itch and damage their skin

He said that his group was interested in how perception modified pain. Sprenger noted that the method might be useful when people scratch at a severe itch and damage their skin.

The German scientists were among 10 winners of Ig Nobel awards, which recognise work that first makes people laugh and then makes them think. Joint winners of the biology prize injected a note of British eccentricity into the ceremony. Charles Foster, who lived in the wild as a badger, an otter, and other animals, won for his book *Being a Beast*, and Thomas Thwaites won for his book *GoatMan*. Thwaites accepted his award dressed as a goat.

The ceremony will be available on YouTube.

Janice Hopkins Tanne New York

Cite this as: *BMJ* 2016;354:i5193

MSF

hit by an airstrike, killing staff and patients. This led MSF to pull staff from six hospitals because it was "neither satisfied nor reassured" by the Saudi led coalition's statement that this attack was a mistake. Alhulail added, "As health professionals, we have a duty to speak out against all causes of ill health in Yemen. This must include the sale and export of UK weaponry that is fuelling the conflict."

Since the war began more than 10 000 deaths have been reported by the United Nations, with the latest estimate indicating that 3800 of those have been civilians, and healthcare facilities have repeatedly become the targets of bombs.

A Foreign Office spokeswoman told the *Guardian*: "We remain deeply concerned about the human rights situation in the country, and a political solution to the conflict remains the priority."

Jacqui Thornton, London

Cite this as: *BMJ* 2016;354:i5261

GMC was wrong to release report

A High Court judge has ruled that a decision by the General Medical Council to release an expert report on a GP's competence to the patient who complained about him was unlawful.

The patient, who had been given a diagnosis of bladder cancer, complained to the regulator about the GP, named only as DB. He claimed that his illness would have been recognised a year earlier had the doctor been doing his job properly.

The GMC commissioned a report from an expert, who decided that DB had fallen below the expected standard, "but not seriously below."

The regulator decided to close the case and sent the patient a one page summary of the 22 page report. The patient applied under the Data Protection Act for a copy of the full report, arguing that he was entitled to it because it contained personal data.

The GMC asked DB for his consent, but he refused saying, that it was sought for the purposes of litigation, and that the patient might publish it to the world at large, affecting his career.

The GMC carried out a balancing exercise and decided to release the report in the interests of transparency and equality. But Mr Justice Soole said that the balancing exercise "fell into error and got the balance wrong."

Clare Dyer *The BMJ*

Cite this as: *BMJ* 2016;354:i5236

FIVE MINUTES WITH . . .

John Ioannidis

The Stanford University professor talks about the problems with meta-analyses

"We have an epidemic of deeply flawed meta-analyses, with the number published each year having increased by more than 2600% over the past 20 years, compared with only 50% for research studies of all types listed on PubMed.

"It has taken a lot of effort to convince physicians and other stakeholders that they should look for real evidence, such as randomised trials, and even more so to look for systematic reviews and meta-analyses on which to base their decisions and not just trust expert opinions.

"But we now recognise that systematic reviews and meta-analyses can also become tools of this same biased, expert based medicine.

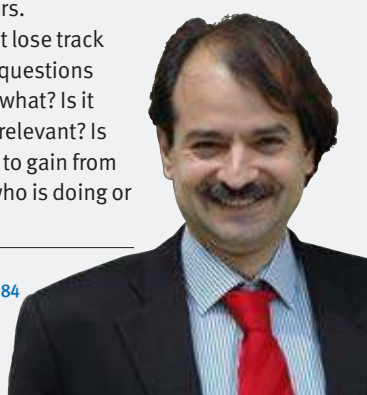
"Systematic reviews and meta-analyses should systematically combine all evidence from relevant studies according to transparent rules and should use formal quantitative methods. No single study can give such a comprehensive view of the potential biases that may exist in a field as a good systematic review or meta-analysis.

READERS SHOULD ASK: SO WHAT? IS IT CLINICALLY RELEVANT? WHO IS FUNDING A STUDY?"

"Problems arise when people underappreciate the biases in the primary studies, don't use the proper methods, have conflicts of interest in getting a particular result or biased interpretation, focus on just getting another publication, and don't pay attention to how many other meta-analyses have been done on the same topic.

"Meta-analyses should be realigned to remove biases and vested interests. And they should be integrated better with primary research. A research agenda should be designed prospectively, with all teams who want to participate joining forces and designing their multiple studies with the explicit plan of sharing data and protocols, being transparent and open, and then combining the data in a meta-analysis that can be verified and scrutinised by outsiders.

"Readers should not lose track of some fundamental questions on meta-analyses: So what? Is it helpful? Is it clinically relevant? Is it biased? Who stands to gain from this? And, of course, who is doing or funding a study?"



Susan Mayor London

Cite this as: *BMJ* 2016;354:i5184

How the BMA lost control of the contract dispute

The BMJ's **Tom Moberly** and **Abi Rimmer** reflect on how the junior doctors' contract dispute has played out

In October 2014, when the BMA's Junior Doctors Committee walked out of negotiations over a new contract, junior doctors were not headline news. Few were engaged in political debates or even aware that plans for a new contract had been under discussion since 2009.

By the time England's health secretary, Jeremy Hunt, announced in August 2015 that he would be imposing a new contract, his jibes at doctors over their supposed lack of commitment and his misuse of weekend mortality statistics created a groundswell of anger. It was this anger that fuelled protests in the streets in October 2015 that were attended by thousands of doctors. But the marches and media campaigns were chiefly led and organised by grassroots groups of junior doctors, not by the BMA.

Rising frustration

For years, junior doctors have been frustrated by the way their training and working lives are organised. With a job that was already stressful, inflexible placements, training requirements, and rota allocations made junior doctors' working lives increasingly difficult.

Discussion on social media, and the work of the grassroots groups, helped bring coherence and focus to these frustrations. At the same time, anger over years of underfunding of the NHS and plans for a seven day service sparked junior doctors into action.

The banners at protests and marches made clear what these doctors were angry about, from "Save our NHS" and "NHS on life support" to "Standing together for the NHS."

But the issues on which these groups focused were far wider than the problems with the contract that the BMA was highlighting. The BMA was focused on reshaping a fixed overall pay bill. Grassroots junior doctors were angry about staff shortages, service cuts, privatisation of the health service, plans for a seven day NHS, and a host of other issues that would not have been solved by renegotiating the junior doctor contract.

HAVE YOUR SAY

What do you think of how the BMA has handled the junior doctors' dispute? Post a rapid response online at thebmj.com.

Once junior doctors had begun a series of strikes in January this year, the BMA seems to have been left struggling to find a negotiating position that would produce a contract that addressed the far reaching concerns of junior doctors.

In May the BMA sought a way out when it negotiated a revised contract that it put to its members and that the chair of the Junior Doctors Committee publicly endorsed. But junior doctors didn't buy it. In a ballot they rejected the revised contract, in large part because it did not resolve the problems they were angry about.

Junior doctors on what BMA should do now

The BMA announced last Saturday that it was planning other action to resist a new contract for junior doctors in England, after it suspended three rounds of strikes. Junior doctors say what they think should happen next

Michael Moran, clinical lecturer and ear, nose, and throat registrar, London

"In the contract dispute, junior doctors are trying to safeguard their patients, as well as the NHS itself. The next steps are crucial, now that industrial action has been suspended by the BMA. The ideal solution would be one that does not threaten patient safety but informs the government and the public about the contribution that junior doctors make to the health service. One solution would be working to rule indefinitely, with strict adherence to set working hours and regular breaks. This should not put any patients at risk but would impact on the volume of service provision, while also demonstrating a wider issue affecting all NHS staff, who so often work many overtime hours with no remuneration."

"We need to make sure we can show the public just how dangerous this is" Benjamin Dean

Benjamin Dean, orthopaedic registrar, Oxford

"The BMA's focus now needs to be on ensuring that a light is shone on the contractual and extra-contractual mechanisms by which unsafe working practices can be highlighted. If the government is going to impose unsafe and dangerous reforms on the general public, we need to make sure we can show the public just how dangerous this is."

Grassroots junior doctors were angry about a host of issues that would not be resolved by contract negotiations

The chair of the committee resigned, and the BMA sought to negotiate a contract that would be acceptable to junior doctors. To get the government back to the negotiating table the committee proposed an escalation of its industrial action.

But many junior doctors had become reluctant to take such drastic action, and at the committee's meeting last Saturday the strikes were called off.

The gap between what junior doctors wanted and the issues that the BMA sought to tackle through contract negotiations has left many junior doctors angry and frustrated. Having chosen not to highlight this gap, the BMA now has to deal with the frustration of junior doctors who are disappointed that many issues affecting their daily working lives remain unresolved.

Tom Moberly, UK editor
Abi Rimmer, BMJ Careers

Cite this as: *BMJ* 2016;345:i5266

Tom Oates, year 8 specialty trainee in nephrology and general medicine, North Middlesex Hospital, London

"The failed escalation of strikes has done significant damage to the credibility of the BMA in general and the Junior Doctors Committee in particular. Any ongoing attempts to resist contract imposition need to focus on improving patient safety and be motivated by a genuine desire to resolve this dispute. For example, encouraging widespread formal incident reporting of rota gaps and unpaid overtime worked for emergency patient care could create a credible national resource that documents the already stretched nature of junior doctors in the NHS."

Pete Turton, year 4 specialty trainee in anaesthesia and intensive care, Mersey Deanery

"I think the BMA have put themselves in a really difficult position. They went for the nuclear option and failed. Working to rule doesn't work, because it's hard to leave the building once you're in. Not doing cremation forms is harsh on the public. I think the BMA should have upped industrial action to 24 hours rather than five days. That might still be an option, but members are getting restless—we've pulled out of industrial action twice now."

Abi Rimmer, BMJ Careers

Cite this as: *BMJ* 2016;354:i5268

HEAT OF THE MOMENT

TAKING THE TEMPERATURE OF THE JUNIOR DOCTORS' DISPUTE

FIVE DAY STRIKES

2 SEPTEMBER 2016 The BMA announces that junior doctors will stage a full withdrawal of labour between 8 am and 5 pm for five days at a time in five separate weeks in the run up to Christmas. The planned action was suspended after a decision by the BMA's Junior Doctors Committee on 24 September

COMPLETE WALK OUT

APRIL 2016 Junior doctors withdraw all labour, including emergency cover, from 8 am to 5 pm on two consecutive days

FIRST ACTION

JANUARY 2016 Junior doctors provide emergency cover only for 24 hours

BALLOT VOTE

NOVEMBER 2015 Nearly all (98%) junior doctors voting in a ballot support strike action over changes to their contract

CONTRACT IMPOSITION

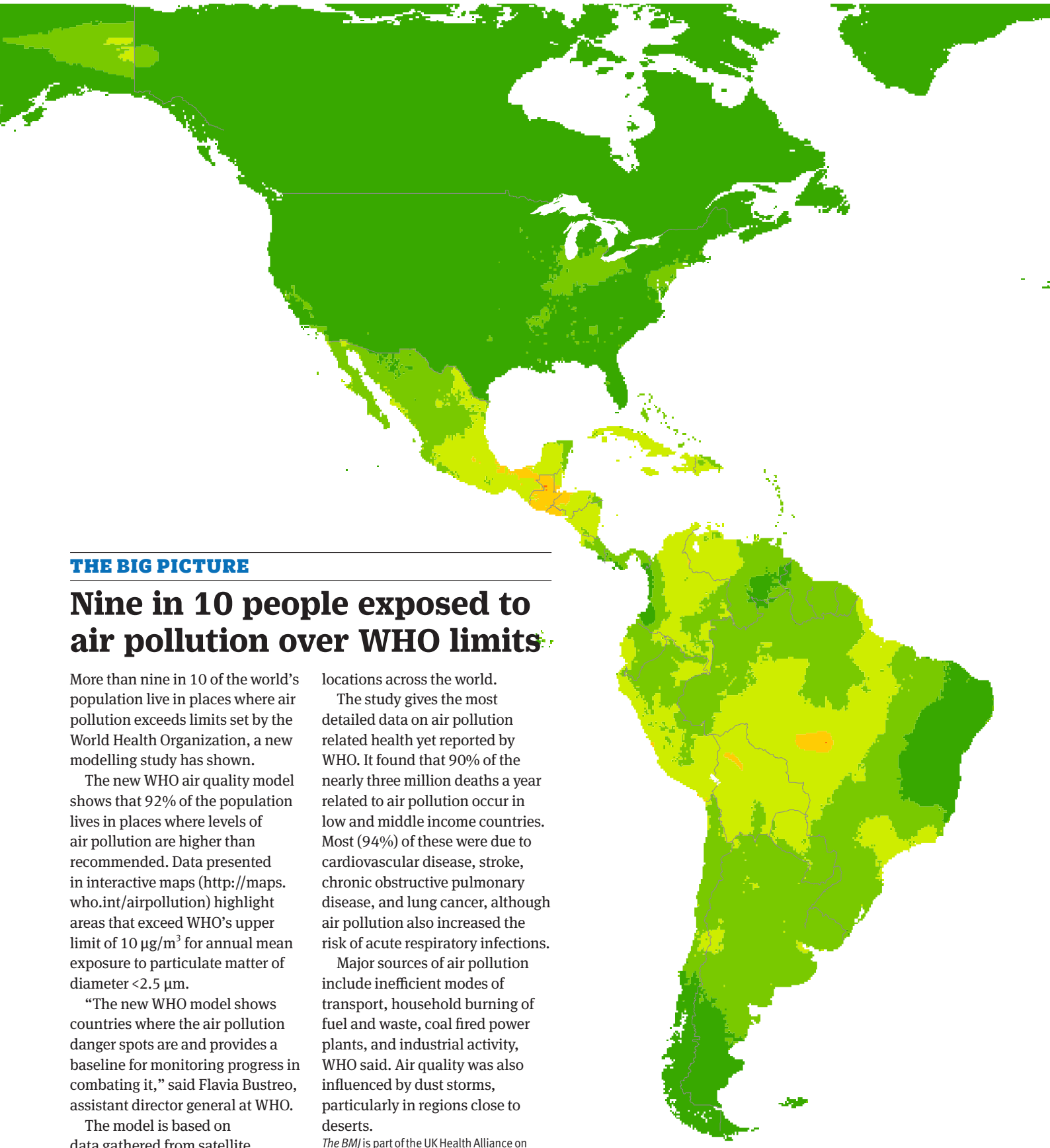
SEPTEMBER 2015 The Department of Health for England says that it will impose a new contract in August 2016. The BMA plans to ballot junior doctors in England over industrial action

TALKS BREAK DOWN

OCTOBER 2014 The BMA announces that negotiations with the government have stalled. The next month the government asks the DDRB to review the contract proposals

TALKS START

OCTOBER 2013 In June 2013 the BMA and NHS Employers agree "heads of terms" for discussion over the junior doctors' contract. In October the two organisations start to discuss the terms of the new contract for UK junior doctors



THE BIG PICTURE

Nine in 10 people exposed to air pollution over WHO limits

More than nine in 10 of the world's population live in places where air pollution exceeds limits set by the World Health Organization, a new modelling study has shown.

The new WHO air quality model shows that 92% of the population lives in places where levels of air pollution are higher than recommended. Data presented in interactive maps (http://maps.who.int/airpollution) highlight areas that exceed WHO's upper limit of 10 μg/m^3 for annual mean exposure to particulate matter of diameter <2.5 μm.

"The new WHO model shows countries where the air pollution danger spots are and provides a baseline for monitoring progress in combating it," said Flavia Bustreo, assistant director general at WHO.

The model is based on data gathered from satellite measurements, air transport models, and ground station monitors at more than 3000 locations across the world.

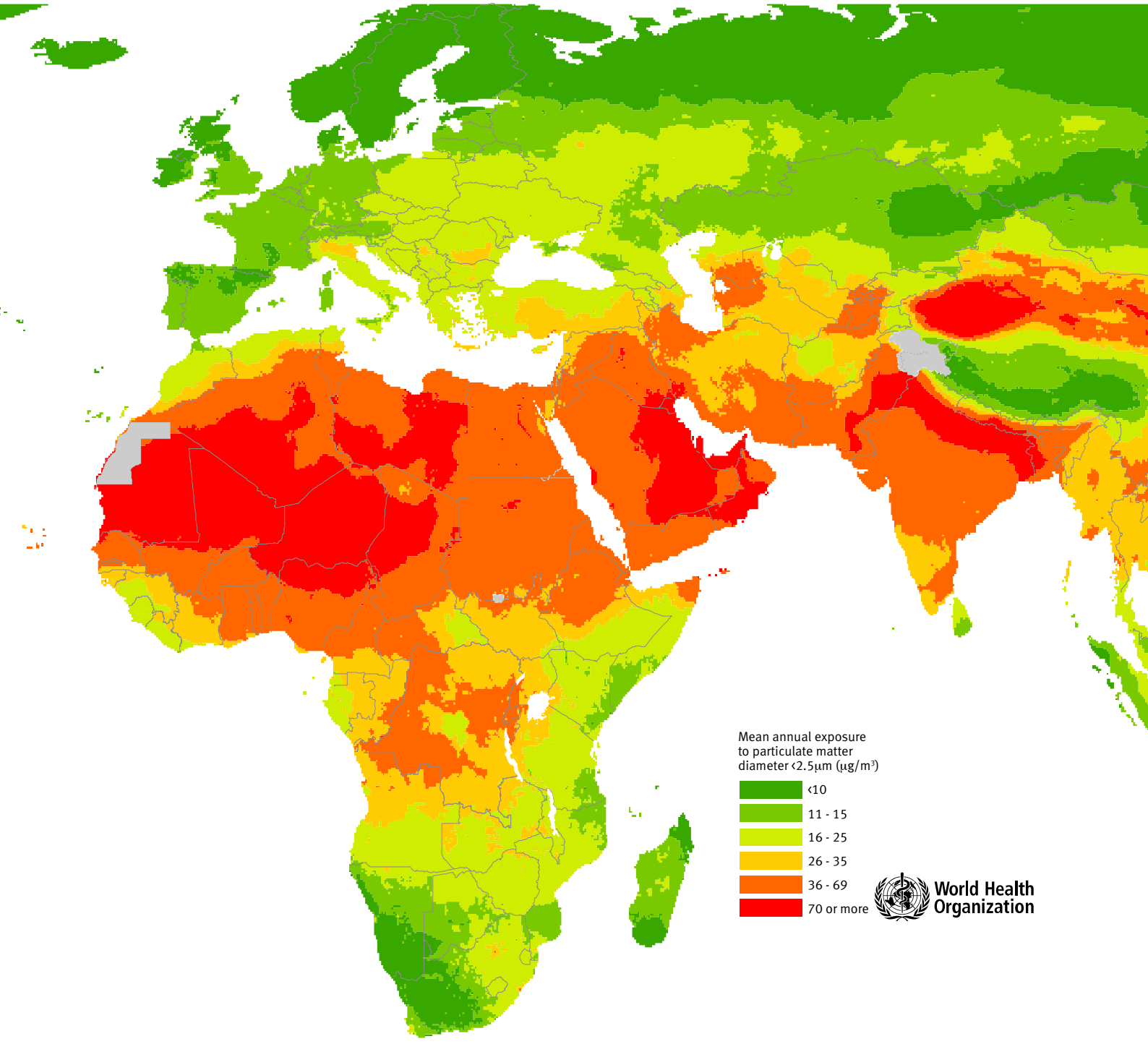
The study gives the most detailed data on air pollution related health yet reported by WHO. It found that 90% of the nearly three million deaths a year related to air pollution occur in low and middle income countries. Most (94%) of these were due to cardiovascular disease, stroke, chronic obstructive pulmonary disease, and lung cancer, although air pollution also increased the risk of acute respiratory infections.

Major sources of air pollution include inefficient modes of transport, household burning of fuel and waste, coal fired power plants, and industrial activity, WHO said. Air quality was also influenced by dust storms, particularly in regions close to deserts.

The BMJ is part of the UK Health Alliance on Climate Change. See www.bmj.com/campaign/climate-change

Susan Mayor, London

Cite this as: *BMJ* 2016;354:i5244



"Air pollution continues to take a toll on the health of the most vulnerable populations: women, children, and older adults" – Flavia Bustreo, WHO

EDITORIAL

Cancer Drugs Fund requires further reform

Reliance on "real world" observational data undermines the evidence base for clinical practice

The reforms to the Cancer Drugs Fund implemented in July were an excellent opportunity to generate evidence on the effectiveness of new cancer drugs.[1] Unlike under the previous arrangements, data on patients' outcomes will have to be collected for all drugs funded by the scheme. However, the reforms' stated reliance on "real world" (observational) data will not generate reliable evidence of effectiveness. We propose an alternative model, using timely randomised controlled trials within routinely collected data sources, to establish which drugs are relatively effective. The current arrangement encourages early access to drugs, with high prices but uncertain benefits, whereas our proposal will provide high quality evidence for future decisions and therefore larger gains in population health.

We propose that expensive new agents are available only within rapid, flexible, and efficient randomised trials

Future proof

Since the reforms, the National Institute for Health and Care Excellence (NICE) is responsible for appraising all new cancer drugs, and the fund will pay for those drugs which have a chance of being judged cost effective, after two years of "real world" data collection.

The central role given to "real world" data is a major cause for concern. Accurate estimates of relative effectiveness requires that outcomes are compared for patients who do, and do not, take the new drug, but who have similar prognostic characteristics.[4] In observational studies, key characteristics are unmeasured and estimates of effectiveness are biased by residual confounding. Also, the conduct of observational studies is more prone to manipulation by those with vested interests. The presumption that, "real world" data can provide unbiased evidence, ignores all we know about good research design for identifying causal effects, and the reasons why well designed randomised trials are the cornerstone of evidence based medicine.[5]

Instead, we propose that NICE makes "only in research" recommendations, whereby these drugs are available only within pragmatic, low cost, randomised trials. These studies should be designed to provide timely, unbiased estimates of effectiveness by routinely randomising patients to the new drug or current practice at the point of NHS care.[6] This can be achieved only with strong support from funders, ethics committees, regulators, and central government, and if a research culture is embedded within the NHS.[7] These trials require clinician time to recruit patients and investment in informatics,[6] but the costs will be low compared with the drug fund's budget. Furthermore, follow-up data can be collected from the UK's high quality, routinely collected clinical datasets (including the world's largest cancer registry), and linked to existing radiotherapy and chemotherapy datasets such as the Systemic Anti-Cancer Therapy dataset[8] and to sources of electronic health records such as the Clinical Practice Research Datalink (CPRD).

The trial designs can be flexible and provide a platform for new drugs as they emerge. Multi-arm, multistage trials, in particular, allow more treatments to be assessed than traditional two arm trials, and enable the range of patient subgroups and treatments to adapt as the data provide insights about which patients respond best to which drugs.[9]

Smarter studies

For some new cancer drugs, an NHS funded randomised trial may provide insufficient additional value to justify the costs.[10] If there is an ongoing trial for regulatory purposes it may be more efficient to delay a NICE decision pending evidence on long term outcomes from the regulatory trial. For drugs for which a trial is judged unethical or impractical, careful non-randomised studies should be conducted to minimise confounding, by collecting longitudinal data on all relevant prognostic characteristics and outcomes for patients receiving and not receiving the new drug. To reduce residual confounding further, studies should collect data on characteristics that predict treatment selection but are unrelated to outcomes.[11]

The reforms to the Cancer Drugs Fund, related initiatives such as the accelerated access review,[12] and comparative effectiveness research using, for example, Surveillance, Epidemiology and End Results (SEER) data linked to Medicare,[13] all rely on "real world" data. These initiatives will undermine the evidence base for clinical practice; once these products are widely used, randomisation will be impossible. Instead, we propose that expensive new agents are available only within rapid, flexible, and efficient randomised trials. Building NHS capacity for this programme would capitalise on the UK's strength in trials, generate long term evidence of value worldwide, and yield large benefits to patients.

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ILLUSTRATION: DUNCAN SMITH

Alan McGlennan, 44, is a consultant anaesthetist and clinical lead at the Royal Free Hospital in London and training programme director for the North Central School of Anaesthesia. On Twitter he lists his biography as "Get up, go to work, push propofol, get showered, go home" and, as his interests, the Hoyo de Monterrey Epicure Especial (a fancy Cuban cigar). More seriously, he writes frequent contrarian articles in the Royal College of Anaesthetists' bulletin, questioning the college's conversion to what it calls perioperative medicine, its record on promoting women in anaesthesia, and the rigidness of training.

BMJ CONFIDENTIAL

Alan McGlennan
Happy despite appearances

What was your earliest ambition?
To play at number 10 for Manchester United, taking over from Lou Macari.

Who has been your biggest inspiration?
Recently it's been Steve Bolsin, known for his whistleblowing work around the Bristol heart scandal. His statue should sit in Richmond House.

What was the worst mistake in your career?
Something I think about at least twice a day. I'll say no more than that.

What was your best career move?
I was the trainee representative on the council of the Royal College of Anaesthetists. An eye and door opener.

Bevan or Lansley? Who has been the best and the worst health secretary?
Bevan was best, but he was no saint. Lansley was pitiful, and Hunt is drowning.

Who is the person you would most like to thank, and why?
Mrs McCoull, my primary teacher at age 7. She realised my misplacement in the set I was in and made me understand my potential.

To whom would you most like to apologise?
See answer #3.

If you were given £1m what would you spend it on?
Anaesthesia and its allied professions have a problem with suicide and drug misuse. I'd spend it on research in that area.

Where are or were you happiest?
Despite how I look and sound, I'm happy all of the time.

What single unheralded change has made the most difference in your field?
Probably intraoperative monitoring. Capnography and pulse oximetry turned the art of anaesthesia into a science.

Do you support doctor assisted suicide?
Yes. As doctors, we're complicit with dehydration, discreet overmedication, letting people languish in demented states, or forcing patients to Dignitas. This isn't right.

What book should every doctor read?
Limits to Medicine by Ivan Illich, a Jesuit priest turned doctor turned academic sociologist. It puts in perspective what we do, but it's not comforting reading.

What poem, song, or passage of prose would you like at your funeral?
Maybe the Wembley hymn, "Abide with Me."

What is your guiltiest pleasure?
The Hoyo de Monterrey Epicure No 2 cigar, although I know that I shouldn't.

What, if anything, are you doing to reduce your carbon footprint?
I sold our second car and had a vasectomy.

What personal ambition do you still have?
Making publicly funded surgical healthcare work within the confines of the NHS in north London. If it can happen here it can happen anywhere.

Do you have any regrets about becoming a doctor?
No, but I'm constantly surprised that I'm here.

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WHAT FUNDING DO THEY GET FROM HEALTHCARE?

Clinton outstripped every presidential candidate by very wide margins in receiving money from almost every sector, from banking to gambling and casinos, said the Center for Responsive Politics. During the 2016 cycle Clinton has received more than $17.1m from the healthcare sector. Trump came in behind seven other candidates to receive $1.3m in donations from the healthcare sector.

THE DEBATE ONLINE AT THEBMJ.COM

The presidential debate that wasn't: Clinton and Trump on healthcare

The 90 minute debate between Hillary Clinton and Donald Trump on 26 September didn't include a single word about healthcare, despite two thirds of US voters saying in a poll that "the future of Medicare and access and affordability of healthcare" were top priorities for the presidential candidates to be talking about.

So what is—and isn't—known about the candidates' positions on various healthcare issues?

Health insurance and "universal care"

Clinton says that she will "defend and expand" Barack Obama's 2010 Affordable Care Act ("Obamacare"), which has cut the number of people without health insurance from 47 million before the act to around 30 million at the beginning of this year. She would allocate $5m (£3.9m) to help enrol those still uninsured into a plan. Trump says he will ask Congress to "deliver a full repeal of Obamacare." He doesn't give specifics about how he will achieve universal coverage but says he will support a plan that "follows free market principles." This contradicts his earlier statements that he would cover everyone under a plan paid for by "government" and that he no longer supports mandatory insurance coverage.

Medicare

Clinton and Trump both support Medicare, the country's national social insurance programme for people aged 65 or over. But Trump's support seems qualified and at times contradictory. He makes no mention of Medicare in his seven point plan for healthcare reform (http://bit.ly/2dw0ev8). At times he has said he would cut Medicare, and at others he said it must be preserved. Clinton says she supports a plan to allow people aged 55 years or older "to opt in while protecting the traditional Medicare program."

Medicaid

Clinton says that 19 states "have left three million Americans without health insurance because their states have refused to expand Medicaid," the insurance programme aimed at people with limited resources (http://hrc.io/2dcH2Dg). She says she will "incentivize" states to expand Medicaid. Trump says he supports taking Medicaid out of the hands of the federal government and turning it over to individual states.

Care for immigrants

Clinton supports expanding healthcare to everyone "regardless of immigration status." Trump says, "Providing healthcare to illegal immigrants costs us some $11bn annually," and that he will enforce laws so that the US has no illegal immigrants.

Healthcare costs

Clinton says she would work with interested state governors to establish a "public option" that would be a government run alternative to private insurance. She says she would cut out-of-pocket expenses for individuals and families by placing unspecified caps on those expenses. Trump wants to allow the sale of health insurance across state lines, which he says would allow "full competition" and force down costs. He also supports "health savings accounts," long favoured by Republicans. The accounts, which can be used only with high deductible insurance plans, allow individuals or families to use a tax free savings account to pay for out-of-pocket expenses.

Prescription drug costs

Both candidates support allowing drug importation from other countries, with quality controls, to lower the costs of prescription drugs. Both say they support allowing Medicare to negotiate drug prices, which is currently prohibited.

Abortion

Clinton wants to "ensure that all women have access to preventive care, affordable contraception, and safe and legal abortion." Trump says that he opposes late term abortion except when the life of the mother is threatened or in cases of rape or incest. He would defund Planned Parenthood as long as it provides abortions and ban any government payments for abortion.

- Clinton's main healthcare statement is at www.hillaryclinton.com/issues/health-care
- Trump's is at www.donaldjtrump.com/positions/healthcare-reform.

Jeanne Lenzer, associate editor, The BMJ

- This is an edited extract of a BMJ blog. Read the full version at blogs.bmj.com/bmj.

Manufacturer failed to disclose faulty device in rivaroxaban trial

An investigation by The BMJ finds that companies were aware of concerns about a faulty device in a regulatory trial. **Deborah Cohen** reports

A drug manufacturer knew about problems with a blood testing device but did not share data before the crucial approval process, an investigation by *The BMJ* has found.

Janssen, the pharmaceutical arm of Johnson and Johnson, withheld data from the Food and Drug Administration about problems with the INRatio device, which was used in the phase III trial (ROCKET AF) of the blockbuster anticoagulant rivaroxaban (Xarelto).

The company generated these data in a safety programme (the Covance recheck) set up after trial investigators became concerned about the accuracy and reliability of the point-of-care device used to monitor patients receiving warfarin.

Janssen also failed to share these data with the safety monitoring board of the trial.

Executives from Bayer—which codeveloped rivaroxaban—were also aware about concerns about the device. However, the German company did not know about the existence of the recheck programme until this year.

Patients in the US are suing Janssen and Bayer for allegedly misleading them over the safety and efficacy of the drug.

In legal testimony, a Bayer official has alleged that Janssen, which had responsibility for conducting and managing the trial, withheld the programme from the company.

Bayer told *The BMJ* that it "expressly contradicts the allegation that Bayer would have withheld safety data."

Janssen said: "We have acted with urgency, diligence and in the best interests of patients and prescribers, sharing data with health authorities and the safety monitoring board of the ROCKET-AF trial."

> "The benefit-risk profile of Xarelto remains positive and unchanged for reducing the risk of stroke in patients with non-valvular atrial fibrillation"
> Janssen

Pivotal trial comes under scrutiny

Published in the *New England Journal of Medicine* (*NEJM*) in 2011, the trial included over 14 000 patients and found rivaroxaban was "similar to warfarin in its ability to prevent" ischaemic stroke or systemic embolism in people with non-valvular atrial fibrillation.[1]

The authors reported there was no significant difference between groups in major bleeding risk—although intracranial and fatal bleeding occurred less often in the rivaroxaban group.

The point-of-care device INRatio—initially marketed by HemoSense and later by Alere—was used to measure international normalised ratio (INR) values in the 7133 participants in the warfarin arm of the study. However, the FDA recalled the device in December 2014 because its INR results could be "clinically significantly lower" than those found by a laboratory method.[2]

However, Janssen and Bayer did not tell the authorities that the device used in the ROCKET trial had been recalled until September 2015.

Global regulators have now launched inquiries; Bayer and Janssen have reanalysed the trial data; the study's executive committee has published two letters in *NEJM* containing its "independent" reanalyses of the data[4 5]; and the US Department of Justice has issued Alere with a subpoena seeking "various documents related to the accuracy, reliability and performance of the INRatio system."[6]

Only the European Medicines Agency has published its full conclusion stating that the defective device would have had only a marginal effect on results.

An FDA spokesperson said that it is "continuing to review relevant data," but it has not changed its recommendations on Xarelto.

The FDA also said that because the INRatio devices were used only to monitor blood clotting rates and adjust the dose of warfarin in the trial, they

WHAT *THE BMJ* REPORTED IN FEBRUARY 2016

- INRatio, the point-of-care device used to monitor warfarin in the control arm of the key pivotal trial underpinning rivaroxaban's approval to prevent ischaemic stroke in non-valvular atrial fibrillation, was faulty and later subject to a class 1 FDA recall
- *The BMJ* alerted regulators and the authors of the trial that was published in the *NEJM*. Janssen said it was the first it had heard of the device recall
- Janssen and Bayer told *The BMJ* their own analyses show the device had not affected trial outcomes; EMA and FDA were still investigating
- Doctors and academics called for the data to be released and independently evaluated

2002

FDA 510(k) clearance of HemoSense INRatio point-of-care INR device

2004

October—Paper published showing that of 8 people with hypertherapeutic INR values 3 were misclassified as normotherpeutic by INRatio[10]

2005

October—FDA sends warning letter to HemoSense stating: "Our review indicates that your firm had information indicating that INRatio devices were generating clinically significant erroneous values"

2006

September—Johnson & Johnson submitted the final protocol, case report forms, and other study documents for regulatory approval of rivaroxaban to the FDA

November—FDA sends warning letter to HemoSense warning of violations, including "failure to investigate complaints involving the possible failure of a device"

December—First patient enrolled in ROCKET AF

2007

February—Members of the ROCKET AF executive committee are said to have expressed concern over the INRatio device and called on Janssen to validate the device or implement study-wide routine quality control procedures, plaintiffs' lawyers allege

July—Bluestein et al publish paper concluding, "POC devices may not be appropriate for commercial laboratory test substitutions without prior performance evaluation"[11]

2008

February—ROCKET AF investigators told in letter from Janssen to contact the medical monitor, Parexel or Duke Clinical Research Institute helpline if they have concerns about INRatio

2010

September—Last patient contact in ROCKET AF

October—Database lock of ROCKET AF

are "confident that the rates of stroke, bleeding, and other clinical outcomes" in patients taking rivaroxaban are correct.

However, the relative risk of stroke and bleeding of rivaroxaban compared with warfarin "could be affected" by the performance of these devices.

Could the regulatory investigations have been avoided?

Shortly after the trial started in February 2007, members of its executive committee raised concerns over INRatio. Following complaints from other trial investigators about the device, Janssen launched the Covance recheck programme in early 2008.

In a letter from Janssen to investigators dated 21 February 2008, the company described a new kit for collecting "special blinded INRs…designed to assist investigators who believe that a subject's INR values…are greatly different from what was expected."

Janssen's letter did not explain the concerns that led the company to send the special kits. Nor was the new recheck programme ever added to the trial protocol.

In March 2016, Janssen's lawyers described the recheck programme as a "component" of the ROCKET trial.

Both Bayer and Janssen have told *The BMJ* that investigators submitted 149 samples to the recheck programme (rivaroxaban 78; warfarin 71). Janssen's legal plea stated that there were "16 instances where the value from the point of care device and lab were recorded as inconsistent."

However, it is unclear how Janssen defined "inconsistent" readings.

Perhaps most alarmingly, Janssen did not tell the FDA about the recheck programme or trial investigators' concerns about the device.

Who was informed?

Despite the safety of trial participants potentially being compromised, Janssen did not give the data generated by the recheck programme to the trial's data and safety monitoring board.

Peter Rothwell, professor of clinical neurology at Oxford University, was a member of the board. He said he has "no memory of the board being told about the programme.

"Clearly, if the sponsor of the trial had concerns about the validity of the point-of-care testing of INR that would have been important for the board to be made aware of."

Hiding in plain sight

There may be reason to believe regulators could have caught the problem themselves.

As part of the ROCKET trial design a split sample was taken from participants at weeks 12 and 24 of the trial. One sample was analysed by the point-of-care device and the other by a central laboratory. The results were kept blinded until the trial finished.

The 12 and 24 week paired sample data were not used to ascertain the accuracy of the device before the drug was approved, but they are central to the current debate over the device's accuracy.

Reviews submitted to the EMA by Bayer and Janssen found that "the potential issue with Alere's monitoring device did not impact the [trial's] conclusions," a spokesperson from Janssen told *The BMJ*, adding: "The benefit-risk profile of Xarelto remains positive and unchanged for reducing the risk of stroke in patients with non-valvular atrial fibrillation."

Peter Rothwell, professor of clinical neurology at Oxford University, was a member of the board. He said he has "no memory of the board being told about the programme

However, these analyses did not include all patients. When the device was recalled in December 2014, the recall notice listed specific patient populations that were more likely to have faulty readings. The companies focused their analyses on these subgroups.

Thomas Marciniak, a former FDA official who was a drug reviewer on Janssen's application to use rivaroxaban in acute coronary syndrome, told *The BMJ* that these analyses are "worthless" because the "inaccuracies are not limited to the recall patients."

And EMA's review—published two days after *The BMJ* investigation in February 2016—seems to corroborate Marciniak's concern. Its analysis of the week 12 and 24 paired samples found "discrepancies of potential clinical relevance" in about 35% of the estimations.

EMA's report further states that warfarin may have been improperly

Patients in the US are suing Janssen and Bayer for misleading them over the safety and efficacy of the drug

2011

14 March—FDA issues Janssen information request relating to performance of INRatio in ROCKET AF

17 March—Janssen's response to information request submitted, which it is claimed does not include Covance recheck programme data nor week 12/24 paired data

8 September—ROCKET AF published in *NEJM*

8 September—FDA advisory committee meeting to discuss approving rivaroxaban. Clinical reviewers express concern about warfarin's time in therapeutic range

22 September—EMA grants marketing authorisation for rivaroxaban

November—FDA grants market authorisation for rivaroxaban.

2014

December—FDA initiates class I recall of the INRatio and INRatio 2 stating: "Device may provide INR results that are clinically significantly lower than results obtained using a reference INR system (laboratory method)"

2015

February—*The BMJ* contacts the EMA about the recalled device used in ROCKET AF

March—Alere confirms that the devices affected by the recall include those used in the ROCKET AF trial

24 September—Alere confirmed to Janssen/Bayer that recall applied to INRatio devices used in ROCKET AF

December—Letter containing the "independent" reanalysis of ROCKET AF submitted to the *NEJM*

2016

3 February—Patel and colleagues' reanalysis published in *NEJM*[4]

3 February—*The BMJ* publishes "Rivaroxaban: Can we trust the evidence?"[9]

5 February—EMA states that: "the safety of Xarelto remains unchanged"[7]

March—Janssen lawyers acknowledge the existence of the Covance recheck programme in the US courts

April—FDA confirms it had previously been unaware of the recheck programme. It asks Janssen for a detailed description of its purpose

May—EMA says it only heard of the recheck programme when contacted by *The BMJ*

dosed in participants whose INRatio readings were lower than the corresponding laboratory value.

To estimate the effect of the misreading, EMA asked Bayer to compare rates between participants whose laboratory results fell within range of the INRatio reading and those whose results were out of range. This found that the larger the difference between the INRatio and laboratory readings, the higher the rate of major bleeding. People whose readings were more than 2 units apart were over 40% more likely to have a major bleed than those whose readings were the same.

Carl Heneghan, professor of evidence based medicine at Oxford University and an author of a forthcoming Cochrane review of direct thrombin inhibitors and factor Xa inhibitors for atrial fibrillation, told *The BMJ* that the INR device errors "are worrying" as there is "a near exponential increase in bleeding risk with increasing INR… some of the normal results were actually INRs above 8, which require active intervention to reduce the risk of bleeding."

Despite all this, the EMA report stated "benefit/risk balance remains unchanged and favourable for treatment with rivaroxaban."

Marciniak described EMA's review as a "whitewash," alleging that the regulator has ignored "the serious device inaccuracies that those analyses reveal."

NEJM reanalysis

Bayer and Janssen have highlighted the "independent reanalysis" by the ROCKET AF executive committee and Duke Clinical Research Institute to support their conclusions that the device malfunction did not affect trial outcomes. This was published as a letter in the *NEJM* in February.[4]

But this letter did not include an analysis of the paired week 12 and 24 data.

After a complaint by Bob Powell, a former FDA pharmacologist, to the *NEJM* in July,[8] stressing the laboratory data at 12 and 24 weeks should be compared with the point-of-care data, Patel and colleagues reanalysed the data. They calculated that 13% of warfarin patients had discordant results at 12 or 24 weeks and 4% at both, and concluded that the new results were "consistent" with their original report.[5]

But much of the debate hinges on what degree of inaccuracy is considered acceptable. In the case of INR point-of-care devices, the FDA has required at least 90% agreement with laboratory INR results.

Patel and his coauthors also reported that in warfarin treated participants with discrepant INRatio and laboratory results, both ischaemic stroke and bleeding rates were higher than in those with non-discrepant results. They argued that the rise in both types of events countered the hypothesis that device malfunction would have led to increased clinical events.

However, Powell told *The BMJ* that some of the ROCKET team's assumptions were wrong: "The incidence of both ischaemic stroke and bleeding increase with warfarin treatment as the INR goes above 4."

He said discrepancies in the INR readings from INRatio did not occur in the same patients at 12 and 24 weeks, and this variation would have occurred throughout the study.

Carl Heneghan, professor of evidence based medicine at Oxford University told *The BMJ* that the INR device errors "are worrying" as there is "a near exponential increase in bleeding risk with increasing INR

Some are also questioning how "independent" these analyses actually are, as employees of both Janssen and Bayer are members of the committee that did the reanalysis. However, in a statement the executive committee said it stood behind the "conduct and rigour" of the study.

Can we trust ROCKET at all?

The problems with INRatio are not the first ROCKET has faced. During the drug's assessment, two FDA clinical reviewers said rivaroxaban should not be approved because of inadequate warfarin control in the trial.

While the FDA continues its investigation, it told *The BMJ* that the device malfunction didn't have a "significant impact"—but it's unclear what this means.

Heneghan remains unsure. "It is impossible to create subgroups that had 'accurate results' based on just two external quality control measures. In addition, the measures of TTR [time in therapeutic range] quoted in the trial results would be worse if the results were based on a lab INR results.

The implications are we still do not know whether this is a safe drug. We need a trial to assess the safety and efficacy of rivaroxaban. Just one caveat—it should be run independently."

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EDITORIAL

Novel oral anticoagulants for atrial fibrillation

Patients must live with uncertainty until we have independent scrutiny of key trial data

Warfarin reduces the risk of stroke in patients with non-valvular atrial fibrillation but has limitations: a narrow therapeutic window, the need for regular monitoring, and risks of bleeding and drug-drug interactions. Partly because of these limitations, novel oral anticoagulants (NOACs or non-vitamin K antagonist) have emerged, including direct thrombin inhibitors, such as dabigatran, and factor Xa inhibitors, such as rivaroxaban. These drugs do not need routine monitoring and are subject to fewer drug-drug interactions. Both have evidence of cost effectiveness in stroke prevention,[1] and in 2014, the UK's National Institute for Health and Care Excellence (NICE) recommended that dabigatran and rivaroxaban should be considered as an "option for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation."[2]

Despite this, use of new anticoagulants has proved to be highly variable in patients most at risk, ranging from 4% to 70% in different areas in England.[3] This may partly be attributable to clinical uncertainty about the balance of benefit to harm.

Making the data available for independent scrutiny should be a mandatory regulatory requirement

Early concerns

Questions remain about the key drivers of this uncertainty. NICE technology appraisals for both dabigatran [4] and rivaroxaban [5] were primarily based on two large, industry sponsored clinical trials, RE-LY and ROCKET AF.[6 7] In RE-LY, rates of stroke, systemic embolism, and major haemorrhage among those taking dabigatran were either the same as or lower than in those taking warfarin. In ROCKET, rivaroxaban was non-inferior to warfarin and was associated with fewer fatal bleeding events and fewer intracranial haemorrhages.

However, there were early concerns that the conduct of the RE-LY trial and the quality of the data may be compromised. The US Food and Drug Administration therefore initially refused to file an approval of the drug for non-valvular atrial fibrillation and requested a review of RE-LY data. This revealed inconsistencies for 3054 participants and identified previously unreported adverse events (32 myocardial infarctions and 69 major haemorrhages).[9]

The validity of the ROCKET AF trial of rivaroxaban has also been questioned.[10] Participants randomised to warfarin were monitored using a defective point-of-care device that was subsequently recalled.[11] It is therefore unclear whether participants in the warfarin arm were managed appropriately, giving a possible unfair advantage to rivaroxaban. Cohen's latest investigation in this issue highlights that some of the ROCKET investigators raised concerns about the faulty device and that the data and monitoring safety board may not have been fully informed about a safety investigation instigated by Janssen, the company running the trial.[12]

Published trials suggest that novel oral anticoagulants, such as dabigatran and rivaroxaban, are non-inferior to warfarin,[13] a finding replicated in routine data collected from observational cohorts.[14] Yet uncertainty remains about the reliability of the evidence. Part of this uncertainty can be traced back to the rapid review approval process, which aims to accelerate the approval of drugs with the potential for significant clinical benefit. However, when a trial's validity is then called into question this may hinder translation, and in some cases, delay wider uptake.[15]

Independent scrutiny

Replication of the results from RE-LY and ROCKET in independent trials would be one way to reduce uncertainty, but this may take several years. In the mean time, making the data available for independent scrutiny should be a mandatory regulatory requirement, particularly when there are questions about trial rigour. Finally, a detailed independent analysis of unpublished data from clinical study reports, similar to previous analyses of neuraminidase inhibitors,[17] would also help. We have requested the relevant clinical study reports from the European Medicines Agency, and it has become clear that there are likely to be challenges for the trial sponsors in condensing large reports into digestible publications.

Although independent replication of trials, data transparency, and detailed analysis of clinical study reports will be arduous and costly, the concerns highlighted by recent investigations have shown how essential these approaches are to increase our confidence in new oral anticoagulants. Meanwhile patients and clinicians must, for now, live with the uncertainty left by the evidence currently available.

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FEATURE, p 13

Manufacturer failed to disclose faulty device in rivaroxaban trial