INFLUENZA UPDATE

As the UK deals with the heaviest winter flu surge since 1999 and the government has allowed use of leftover 2009 pandemic vaccines, **Adrian O'Dowd** pulls together the latest information

What is the mix of viruses this year?

The influenza viruses around this year are 2009 H1N1, influenza B, and some sporadic H3N2.

How many deaths and cases have there been so far?

Between 5 September (week 36) 2010 and 6 January (week 1) 2011, 50 deaths associated with influenza infection have been reported across the UK. Most of those who died had not been immunised.

Of the 50, 45 people died with H1N1 and five with the flu type B strain. The deaths have been mainly in younger adults and children with five individuals less than 5 years of age; eight from 5 to 14 years; 33 from 15 to 64 years; and four older than 64 years.

It is important to put this into perspective. A normal seasonal flu kills around 5000 people in the UK, although in 1999-2000 there were 19 000 deaths related to flu. This winter has seen the highest spike in cases since 1999-2000.

How are flu deaths counted?

The flu death figure is only a snapshot of those that will die with or from flu this year and cannot be precise. The details given in the flu report are only cases that the Health Protection Agency has been made aware of.

Ordinarily in a flu season, the agency does not give mortality data—the figures for "flu deaths" come from the Office for National Statistics and are referred to as "all cause excess deaths." This method has limitations since it looks only at excess deaths, and does not examine causation directly.

It is incorrect to say that these are flu deaths, but there is a correlation between "bad" flu seasons when there is lots of flu circulating and an increase in excess mortality.

Professor John Watson, head of the respiratory diseases department at the agency, says: "There is more than one way of counting flu deaths. People who get flu and who subsequently die don't go into hospital with flu tattooed on their forehead.

"We never know exactly how many people have died from flu. Someone might die as an immediate consequence of overwhelming flu or with an illness that has been exacerbated by flu or as a complication of flu.

GEOFF MOORE/REX

Steve Bick, a general practitioner in Dorset, pictured last week when his practice was running out of seasonal influenza vaccinations

"Normally we try to determine the excess of deaths that have occurred in the winter over and above those deaths that would have been expected to occur had there not been flu around. During the [swine flu] pandemic, it was different because it occurred at a time [the summer] when there was not the complication of things that occur during winter and it was not hitting elderly people but young people.

"We did our best to identify and count those deaths that occurred where confirmed flu infection had been reported. We recognised that would not identify all such deaths. It was an underestimate, but it was important information because it gave us an idea of the characteristics of the people who were dying.

"With this season and with the same H1N1 virus causing the trouble and with deaths in young people being reported as an early feature of this rise in flu, we were asked to count again such cases and we are counting them in broadly the same way."

What proportion of the UK population was infected by swine flu in 2009?

Precise figures are difficult to produce. More than 1.1 million people in England collected antivirus drugs in 2009 after being diagnosed by the National Pandemic Flu Service, but there was doubt over how many actually had the virus. A freedom of information request later showed that of 16 560 people swabbed, 1932 tested positive—around 12%.

How many died and how many were admitted to hospital with proved H1N1 infection?

During the flu pandemic of 2009, 474 people died from H1N1 in the UK. The rate of consultations peaked in July 2009 with just over 150 consultations per 100 000 population.

According to the last briefing issued by former England chief medical officer Liam Donaldson in April 2010, 848 patients suspected of having flu were admitted to hospital in England during the pandemic.

Does previous infection with H1NI in 2009 confer resistance in 2011?

The H1N1 virus we have now is virtually unchanged from that present in 2009. Normally, when a person has got a natural flu infection, they should get longlasting cross-reacting immunity from that infection. However, it is uncertain whether all viruses behave like this.

The Health Protection Agency's Professor Watson says: "We don't have information about people who may have been ill twice, so it's something one has to speculate about.

Given the amount of infection that we are seeing this winter it's possible that an infection in 2009 might not provide longlasting immunity, but that's only speculation," he said.

Why did the government fail to get the word out about vaccination?

Health secretary Andrew Lansley decided to axe the usual autumn public awareness advertising campaign to urge people to get the flu jab in 2010. Mr Lansley said that he was unconvinced it would make any difference and that leaving it to local GPs to target at-risk groups was more appropriate.

After growing pressure during the winter and a spike in the number of flu cases, the government relented and relaunched the *Catch it, Bin it, Kill it* television, radio, and press advertising campaign on 1 January.

Dr Meirion Evans, a consultant epidemiologist with Public Health Wales and the Faculty of Public Health spokesman for health protection issues believe that the vaccination campaign has been handled appropriately.

"Part of the problem is the media are tending to treat this year's flu season rather more like the pandemic flu we experienced [in 2009]," he says."If you take a longer term perspective on it, what we are seeing is flu occurring within the winter season in a similar pattern to what we normally see during flu seasons but rather more than we have seen in recent years. Vaccination coverage levels are comparable to previous seasons, although they are not as high as we would like."

What's happening elsewhere in the world?

In Europe nine other countries have reported influenza activity, primarily associated with influenza H1N1 (2009), including Belgium, France, and Portugal, where there has been widespread activity.

In the USA and Canada overall influenza activity has increased, associated primarily with influenza A (H3N2) and B viruses.

Where do vaccination rates stand at the moment?

Rates of uptake of vaccine this winter are similar to those last year. By week 52, the proportion of people aged 65 or over who had received the seasonal trivalent jab was 70%.

For those under 65 in an at-risk group it was 45.4%. Among pregnant women, who have been advised to have the vaccine for the first time this year, the uptake rate is about 40%. Uptake among healthcare professionals remains low at around 20%.

How are vaccine stocks lasting?

More than 14 million doses of seasonal flu vaccine have been distributed in the UK this season, but there has been a late surge of eligible people coming forward for vaccination.

Local shortages have been reported of the seasonal flu vaccine, which gives protection against the three viruses: influenza B, H3N2, and H1N1.

The Department of Health announced on 6 January that GPs would be given immediate access to 12.7 million doses of the H1N1 vaccine Pandemrix left over from the 2009 pandemic and issued a letter explaining how to access it.

This was to ensure that everyone at risk could be immunised against the main circulating virus this winter. The intent is for GPs to use this vaccine if they are unable to access the normal seasonal vaccine.

Speaking at a briefing, Professor Sally Davies, the interim chief medical officer for England, disagreed that GPs had ordered too little vaccine last April to cover at-risk patients. Rather, it was a case of a "mismatch," with some areas having too much vaccine and others too little.

The Department of Health has said that a review of how flu vaccines are purchased is now under way and whether there is a need for this to happen centrally rather than through GPs.

Why is the government on the back foot?

Much media attention has been focused on flu this winter as a consequence of the weekly reporting of flu deaths, which is still a relatively new phenomenon that began with the 2009 pandemic.

The Faculty of Public Health's Dr Evans adds: "We've had a decade of very low flu activity and this is as high as it's got since 1999, but it still remains within the normal parameters albeit at the upper end of those for winter flu activity."

Dr Evans believes it might be better in the future to change flu immunisation arrangements so that the health departments of England, Scotland, Wales, and Northern Ireland would take responsibility away from GP practices for ordering and paying for vaccines for the coming winter—as happens with childhood vaccines.

What about the role of antivirals this year?

The Department of Health has written to all doctors encouraging them to use antivirals, following National Institute for Health and Clinical Excellence guidelines, for people who are in high-risk groups or people who they judge to have flu.

By contrast with previous years (apart from during the 2009 pandemic) in which very few antivirals have been used in the UK for flu, it is likely we will see a lot more being used in line with the 2009 experience.

Adrian O'Dowd freelance journalist, Margate
adrianodowd@hotmail.com

Cite this as: *BMJ* 2011;342:d190

RESOURCES

Health Protection Agency's Weekly National Influenza Report – www.hpa.org.uk

Royal College of General Practitioners' Communicable and Respiratory Disease for England and Wales—www.rcgp.org.uk

Chief medical officer's update in April 2010 regarding numbers of people who died with flu during the pandemic and numbers admitted to hospital critical care with flu– www.dh.gov.uk

FROM BMJ.COM **Liz Wager**

Wakefield: should we demand public access to raw data?

The latest chapter in the sad saga of the Wakefield et al paper on the measles, mumps, and rubella (MMR) vaccine raises some difficult questions about access to individual patient data.

It is possible that the apparent discrepancies between the patient records and the data in the publication might have come to light much sooner, perhaps even before publication, if the raw data had been available for public scrutiny.

Perhaps journals should demand that authors must make their raw data available on a public website? This might seem a logical way of preventing fraud and misleading reporting, but it's fraught with problems.

For a start, the data in the Wakefield et al paper were from a small case series of children with a relatively uncommon presentation. Such data, as Brian Deer's investigation has shown, are extremely hard to anonymise. I cannot see how such data could have been made publicly available without breaching the traditional confidentiality between doctors and patients.

But if we can't make individual data from small case series available, perhaps we can safely do it for large clinical trials? Apparently not: in countries such as the United States, where electoral registers are freely available, experts say it's possible to identify individuals armed only with a couple of details such as age and location.

Perhaps we could entrust the data to a few trustworthy experts such as peer reviewers? But that's not workable either. Some studies involve millions of data points and most reviewers do not have the expertise, the time, or probably the computer capacity to tackle this. Neither do journals.

At the Committee on Publication Ethics (COPE), we are revising our flow chart on how to handle suspected fabrication by removing the suggestion that editors should request raw data. Experience has taught us that this is simply not feasible. Journal offices are not equipped for this type of forensic examination of data, which can probably only be handled by largish research institutions or specialist investigators.

My only shred of hope lies with the "et als"—let's hope this case might frighten coauthors into taking proper responsibility and never putting their names on papers unless they have had close contact with the underlying data.

Liz Wager is a freelance medical writer, editor, and trainer. She is the current chair of the Committee on Publication Ethics (COPE).

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HOW THE VACCINE CRISIS WAS MEANT TO MAKE MONEY

In the second part of a special *BMJ* series, **Brian Deer** reveals a secret scheme to raise huge sums from a campaign, launched at a London medical school, that claimed links between MMR, autism, and bowel disease

John Walker-Smith, professor of paediatric gastroenterology, hurried to Malcolm ward on the sixth floor of the Royal Free Hospital, London, with what any doctor would think was bad news. An 8 year old boy, admitted for five days of investigations, had been provisionally diagnosed with Crohn's disease. But when the child's mother—here anonymised as "Mrs 2"—years afterwards recounted what happened, she seemed pleased to have received information she expected, and made it sound as if Walker-Smith was glad too.

"He skipped into that room like a 2 year old," she told me. She remembered he said: "[Mrs 2], you were right."

Brightly painted with murals, Malcolm ward was Walker-Smith's. It came with his employment contract. Exactly one year previously, in September 1995, he had been lured to the Royal Free with many perks, of which this was one. Previously the hospital had no children's bowel service, but with him, it had a chance of the best.

The initiative to recruit him, however, had not come from management. It came from an academic researcher in the gastroenterology department: a former trainee surgeon, Andrew Wakefield.[1] He wanted Walker-Smith, who would bring access to children's gastrointestinal tracts, to help him prove a personal theory. This

October 1988: The three in one measles, mumps, and rubella vaccine is introduced to the UK after successful use in the US since 1971. Previously, single measles and rubella vaccines were used, and there was no licensed mumps vaccine

Virginia Bottomley, the then Conservative health secretary, in 1994 launching the multi-million pound MMR vaccination campaign with Professor Sir Kenneth Calman, chief medical officer for England at the time

September 1992: The UK Departments of Health withdraw two brands of MMR vaccine after research shows them to be associated with a raised incidence of transient mumps meningitis, although much lower than with natural disease

January 1994: A campaign group, JABS, is launched in Wigan, Lancashire, alleging that MMR causes brain damage and other problems in children. Autism and inflammatory bowel disease are not initially claimed

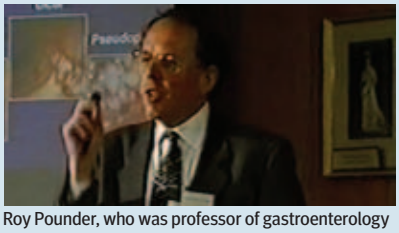
March 1995: Andrew Wakefield, a researcher at the Royal Free medical school, files for a patent claiming that Crohn's disease and ulcerative colitis may be diagnosed by detecting measles virus in bowel tissue and body fluids

September 1995: Paediatric gastroenterologist John Walker-Smith moves with most of his team from Barts hospital, London, to set up a service at the Royal Free

February 1996: JABS solicitor, Richard Barr, retains Wakefield, at £150 an hour, plus expenses, to support a speculative legal attack on MMR manufacturers. This contract is not publicly disclosed

July 1996: The first child is admitted to the Royal Free for research to try to show a link with MMR. The research is commissioned by, and supported with £50 000 from, the UK Legal Aid Board, but this is not publicly disclosed

September 1996: Wakefield and his mentor Roy Pounder meet medical school managers to discuss market projections for a new business based on purportedly diagnosing Crohn's disease from the presence of measles virus



Roy Pounder, who was professor of gastroenterology at the Royal Free

"You used to hear Wakefield's people talking about how they would win the Nobel Prize"

was that Crohn's disease was caused by persisting measles virus infections[2]—most notably, he came to suggest, from vaccines.[3]

"You used to hear Wakefield's people talking about how they would win the Nobel Prize for this," remembers Brent Taylor, the Royal Free's head of community child health, who frequently clashed with the pair. "The atmosphere here was extraordinary."

But instead of honours, the two men reaped disgrace. In January and May 2010, the UK's General Medical Council found them guilty of a raft of charges over a project involving child 2.[4] Wakefield, now 54, was judged by a five member panel to be guilty of some 30 charges, including four counts of dishonesty and 12 of causing children to be subjected to invasive procedures that were clinically unjustified. Walker-Smith, 74, was deemed irresponsible and unethical.[4] Both were struck off the medical register[5 6] and have since filed High Court appeals.

Working on a lawsuit

Their misconduct arose out of a fishing expedition, in which Malcolm ward was the pond for the measles theory. Since February 1996, seven months before child 2's admission, Wakefield had been engaged by a lawyer named Richard Barr, who hoped to bring a lawsuit against vaccine manufacturers.[7 8] Barr was a high street solicitor, and an expert in home conveyancing,[9] but also acted for an anti-vaccine group, JABS. And, through this connection, the man nowadays popularly dubbed the "MMR doctor" had found a supply of research patients for Walker-Smith.

"The following are signs to look for," Barr wrote in a newsletter to his vaccine claim clients, mostly media enlisted parents of children with brain disorders, giving a list of common Crohn's disease symptoms. "If your child has suffered from all or any of these symptoms could you please contact us, and it may be appropriate to put you in touch with Dr Wakefield."

The first to be admitted—in July 1996—was a 3 year old boy with autism. But, according to his records, reviewed by the GMC panel, he was so constipated that, despite two attempts, the endoscopist could not reach his small intestine. So child 2, who had diarrhoea (found to be constipation overflow) was the first to have his ileum intubated.

Child 2 also had autism, the first signs of which came on "a few months" after MMR vaccination.[10] His mother was referred to Wakefield by the JABS organiser, and the boy would not only be the lead test case in Barr's eventual, failed, lawsuit but would feature with 11 other children in a now notorious, retracted, *Lancet* paper linking the vaccine with bowel and brain problems.[11]

He was admitted on Sunday 1 September 1996 and endured a gruelling battery of investigations.[4] These included magnetic resonance imaging of his brain, electroencephalography and evoked potentials, radioactive Schilling test, blood and urine tests, and lumbar puncture—all specified in an agreement with Barr.[12]

A viral diagnostic

The following day, Monday, child 2 had an ileocolonoscopy, which, in common with seven other children reported in the paper, the GMC panel would find was not clinically warranted. Tuesday was Wakefield's 40th birthday. And on Wednesday, with the

Single vaccine patent filed by Wakefield

June 1997: Claiming that the measles virus in MMR causes problems, Wakefield files for a patent on a "safer" single measles vaccine and for products to treat both autism and inflammatory bowel disease. This, too, is not publicly disclosed

February 1998: The *Lancet* publishes a 12 patient case series by Wakefield and 12 others, proposing a link between MMR and a "new syndrome" of autism and bowel disease. At a press conference, he urges the use of single vaccines instead of MMR

February 1998: Just days after the press conference, Wakefield and business partners meet Royal Free medical school managers to discuss a joint company to develop products based on his MMR claims, including "a replacement for attenuated viral vaccines"

Wakefield (centre) at the press conference to launch the *Lancet* research

Wakefield and his wife Carmel, after whom the doctor named one of his health businesses

February 1999: Unigenetics is incorporated, with Wakefield and a Dublin pathologist, John O'Leary, as directors. The company is awarded £800 000 by the Legal Aid Board to perform tests on samples from children seen at Walker-Smith's Royal Free unit

December 1999: Mark Pepys, new head of medicine at the medical school, challenges Wakefield about his business scheme and puts him on notice that he must replicate his research

January 2001: The *Daily Mail* and other newspapers launch campaigns backing Wakefield, working with JABS, after he publishes a purported review of his evidence and repeats his calls for single vaccines

October 2001: Wakefield is asked to leave the Royal Free after failing to mount a large scale controlled study to confirm or refute his claims about MMR

December 2001: Prime Minister Tony Blair is ambushed by Wakefield supporters, who claim that his youngest son, Leo, did not have MMR. The Blairs initially decline to comment but much later deny the claim

news that the boy—still on the ward—might have Crohn's disease, the doctor produced a remarkable document. It was an 11 page draft of a scheme behind the vaccine scare, now revealed for the first time in full.

The document was headed "Inventor/school/investor meeting 1." Based on a patent Wakefield had filed in March 1995 claiming that "Crohn's disease or ulcerative colitis may be diagnosed by detecting measles virus in bowel tissue, bowel products or body fluids,"[13] it proposed starting a company that could reap huge returns from molecular viral diagnostic tests. It predicted a turnover from Britain and America of up to £72.5m a year.

"In view of the unique services offered by the Company and its technology, particularly for the molecular diagnostic," the document noted, "the assays can command premium prices."

To help finance the scheme, Wakefield looked to the government's legal aid fund—meant to give poorer people access to justice. For the previous seven months, child 2 had been enrolled with Barr's firm,[14] which since February 1996—two years before the paper's publication—had been paying the researcher undisclosed fees of £150 an hour, plus expenses.[8]

"The ability of the Company to commercialise its candidate products," the draft plan continued, "depends upon the extent to which reimbursement for the cost of such products will be available from government health administration authorities, private health providers and, in the context of the molecular diagnostic, the Legal Aid Board."

As it turned out later, child 2 did not have Crohn's disease, but three weeks after drafting the plan, Wakefield met three others to discuss it. One was his mentor, Roy Pounder, the Royal Free's professor of gastroenterology and later vice president of the Royal College of Physicians. The others were Bryan Blatch, the medical school's secretary, and Cengiz Tarhan, its finance officer.

Money from the lawyer

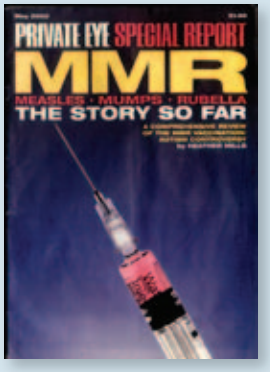
Discussions about the business continued over the following years, but Wakefield's involvement with Barr was quickly noted. In October 1996, the medical school's dean, Arie Zuckerman, a virologist, was told that the lawyer had offered to pay the school for a "clinical and scientific study,"[15] and had sent a first instalment of £25 000.[4] This was held in suspense while Zuckerman sought confidential ethical advice from the British Medical Association, although Wakefield had already started spending it.

"Arising from recent widespread publicity given to this research," Zuckerman (who told me he does not want to discuss these matters) wrote of Wakefield's already televised claims about Crohn's disease, "the Legal Aid Board has provided funding through a firm of solicitors representing Crohn's disease sufferers and we have been asked to make an appointment to the staff of the Medical School, specifically to undertake a pilot study of selected patients."

The BMA answered fully the following March, after its ethics committee had considered the issue. It said that money could be accepted provided there was proper research oversight and transparency over funding and patient sources.

But the dean remained concerned and so

May 2002: Amid continuing media campaigns over MMR, particularly by the Mail and Telegraph groups, the magazine *Private Eye* issues a special edition, written in collaboration with families that are suing vaccine manufacturers



January 2003: Vaccination among 2 year olds falls to 78.9%: below the 92% the Department of Health says is needed to maintain herd immunity. Figures in parts of inner London are half the national rates

September 2003: The Legal Services Commission stops funding for Barr's lawsuit after barristers for the claimants report to the commission that, on the evidence, they cannot make a case that MMR causes autism


Richard Horton, *Lancet* editor

February 2004: The *Sunday Times* reveals that the Legal Aid Board funded the *Lancet* research and that many of the children were litigants. Richard Horton, the journal's editor, rejects more serious charges against the authors, later proved by the GMC

March 2004: Ten of the 1998 paper's 13 authors, excluding Wakefield, retract its "interpretation" section, which claimed an association in time between MMR, enterocolitis, and regressive developmental disorders

November 2004: Channel 4's *Dispatches* reveals Wakefield's single vaccine patent and that, despite Wakefield's claims that the culprit for the disorders is measles in MMR, molecular tests in his laboratory found no trace of the virus


Brian Deer questions Wakefield as part of the Channel 4 *Dispatches* programme

January 2005: Wakefield initiates libel lawsuits, funded by the Medical Protection Society, against the *Sunday Times*, Channel 4, and Brian Deer over Deer's website, claiming that all allegations are false and defamatory

March 2005: Among much research rejecting any link with developmental disorders and bowel disease, research is published showing that, after MMR was discontinued in Japan, the incidence of autism diagnoses continued to rise

October 2005: In the London High Court, Mr Justice Eady refuses an application from Wakefield to freeze his libel actions and orders him to proceed to trial of Deer's allegations against his "honesty and professional integrity"

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Listen to Brian Deer explain the background to his MMR investigation in this week's podcast at bmj.com/podcasts

made an arrangement with the hospital's chief executive, Martin Else, who managed a charity called the Special Trustees. Else, now chief executive of the Royal College of Physicians (who told me that he was "not aware of any significant issue being raised"), agreed that the charity could take Barr's payment and hold it as a grant for Wakefield. So the legal money (which eventually totalled £50 000 and seed funded the business scheme) was moved from the medical school into a numbered hospital charity account and then paid out for Wakefield's research on the MMR vaccine—back in the medical school.[4]

"Further to our conversation regarding the establishment of a fund with the Special Trustees for your income and expenditure associated with the MMR research," Else wrote to Wakefield, "I can confirm that a grant will be established for the purpose, given your written confirmation that there is no conflict of interest involved."[16]

Wakefield obliged, but the arrangement raised issues about the two institutions' involvement in the vaccine crisis. For when the *Lancet* paper was published, in February 1998, and the scare was launched at a televised press conference, nobody was aware that Wakefield was receiving substantial personal payments from Barr.[1] But both the medical school's dean and the hospital's chief executive knew that his research was part funded through a lawyer.

The paper itself, meanwhile, included a funding statement, which Else later told me he did not notice. "This study was supported by the Special Trustees," it said, with no mention of legal aid or Barr.

The lawyer, however, was forthright when later asked. He said he paid for the *Lancet* research. "I remember noting at the time that the funding acknowledgment wasn't there," he told me. "But it didn't seem to be a big deal, because it just wasn't a big deal in those days."[17]

Behind the press conference

Neither school nor hospital stood on the sidelines. They threw their weight behind Wakefield. In the build-up to the press conference, they installed extra phone lines and answering machines to field the expected panic, and distributed to broadcasters a 23 minute video news release showcasing Wakefield's claims. "There is sufficient anxiety in my own mind for the long term safety of the polyvalent vaccine—that is, the MMR vaccination in combination—that I think it should be suspended in favour of the single vaccines," he said, in one of four similar formulations on the videotape.[18]

The press conference and video boosted the commercial plans, which were moving forward behind the scenes. The following week, Wakefield brought two associates to the school for an already scheduled meeting with the finance officer Tarhan. One was the father of child 10 in the paper. The other was a venture capitalist. And two days after the meeting, they submitted a 13 page proposal to launch a joint business with the school. It would be focused on a new company, Immunospecifics Biotechnologies Ltd, aiming not only to produce a diagnostic test, as proposed 18 months earlier, but also "immunotherapeutics and vaccines."

Given the previous week's publicity drive, the vaccine plans were sensitive. But the


Schoolboy, 13, dies as measles makes a comeback

April 2006: As measles outbreaks are reported across Britain, the first death in the UK from the disease in 14 years is reported—a 13 year old boy from the traveller community

December 2006: The *Sunday Times* reveals Wakefield's personal funding from Barr to support the lawsuit over MMR: £435 643 plus expenses, from the legal aid fund. Some other Royal Free doctors were also paid

January 2007: Two days after the payments from Barr are revealed, the Medical Protection Society stops funding for Wakefield's libel actions and agrees to pay the defendants' costs of about £800 000 on top of its own legal bills

July 2007: At a fitness to practise hearing in London, the General Medical Council opens its case alleging serious professional misconduct by the *Lancet* paper's three senior authors, Wakefield, Walker-Smith, and endoscopist Simon Murch

February 2009: The *Sunday Times* alleges that Wakefield "fixed" the appearance of a link between MMR and autism. He denies fraud and files a complaint with the UK Press Complaints Commission, which he later abandons

February 2009: In the United States, three test case judgments for 5000 claims based on Wakefield's theories are handed down in federal court, rejecting the allegation that MMR can cause autism. They are upheld on appeal in August 2010

January 2010: A panel comprising three doctors and two lay members gives findings of fact on the GMC's case, upholding dozens of charges against Wakefield, Walker-Smith, and Murch and sending all three forward for sentencing

February 2010: Six years after the matters were raised with the *Lancet*, the journal fully retracts the 1998 paper. Horton describes aspects of it as "utterly false" and says he "felt deceived"

May 2010: After a 217 day inquiry, the GMC panel orders Wakefield and Walker-Smith to be erased from the medical register, but notes that Murch had shown "insight" and finds him not guilty of serious professional misconduct

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- Brian Deer: Piltdown medicine—The missing link between MMR and autism
- Liz Wager: Does the Wakefield et al case mean we should demand public access to raw data?

school had long known of this ambition. First surfacing in Wakefield's 1995 patent for a diagnostic test for Crohn's disease, it had been fleshed out in 1997, eight months before the press conference, in a patent for a "safer" single measles shot.[19]

The revised business plan was ambitious and detailed, aiming to raise £2.1m from investors. It spanned the detection of Crohn's disease, the treatment of autism, and "a replacement for attenuated viral vaccines."

The methods for the molecular test for Crohn's disease were newish. But those for the treatment and vaccines were dated. They relied on transfer factor, a largely abandoned fringe technology to move immune cells from person to person.[20]

Nevertheless, the school remained interested, and a two year courtship ensued. Even as the vaccine scare escalated, triggering a deluge of referrals to Walker-Smith, staff at Freemedic, the commercial arm of what was now the merged Royal Free and University College Medical School, poured over contracts and plans.

Trading was to be fronted by Carmel Healthcare Ltd—named after Wakefield's wife. Firmly rooted in Barr's lawsuit, which eventually paid Wakefield £435 643, plus expenses,[21] the business was to be launched off the back of the vaccine scare, diagnosing a purported—and still unsubstantiated[22]—"new syndrome." This, Wakefield claimed, comprised both brain and bowel diseases, which, after Crohn's disease was not found in any of the *Lancet* children, he dubbed "autistic enterocolitis."[23]

"It is estimated that the initial market for the diagnostic will be litigation driven testing of patients with AE [autistic enterocolitis] from both the UK and the USA," said a 35 page "private and confidential" prospectus, which was passed to me by a recipient. It was aimed at raising an initial £700 000 from investors and forecast extraordinary revenues. "It is estimated that by year 3, income from this testing could be about £3 300 000 rising to about £28 000 000 as diagnostic testing in support of therapeutic regimes come on stream."

Carmel was registered in the Irish Republic, where Wakefield would also become a director of another business. This was Unigenetics Ltd, incorporated in February 1999 with a Dublin pathologist, John O'Leary. After Wakefield submitted a confidential report to the Legal Aid Board,[24] Unigenetics was awarded—without checks—£800 000 of taxpayers' money[21] to perform polymerase chain reaction tests on bowel tissue and blood samples from children passing through Malcolm ward.

The key players in Carmel were the same as in the first company, Immunospecifics, with their planned equity now set out. Wakefield would get 37%, and the father of child 10 22.2%. The venture capitalist would get 18%, Pounder 11.7%, and O'Leary 11.1%.

Some would also be awarded extra money in advance, in proposed "executive and non-executive staff costs." Wakefield was set to get £40 000 a year,[25] in addition to his legal earnings and medical school salary, with an annual travel budget of £50 000 for the business.

Here was another striking conflict of interest, but Wakefield had long made clear his expectations. "The Company will endeavour to ensure that the principal members of its management and scientific team are suitably incentivised by the allocation of Equity and stock options," he had written in September 1996, when child 2 was still on the ward.

Carmel was to be based at the Coombe Women's Hospital, Dublin, where legal aid money paid for a laboratory. A prospectus described a public relations effort aimed at two "target" audiences: "parent groups and lawyers representing affected individuals" and "major pharmaceutical companies."

"Once the work of Professor O'Leary and Dr Wakefield is published, either late in 1999 or early in 2000, which will provide unequivocal evidence for the presence of the vaccine derived measles virus in biopsy samples," the prospectus said, "the public and political pressure for a thorough, wide ranging investigation into the aetiology of the bowel conditions will be overwhelming.

"As a consequence of the public, political and legal pressures brought to bear, the demand for a diagnostic able to discriminate between wild type and vaccine derived measles strains will be enormous."

Keeping it secret

To facilitate negotiations, letters and draft contracts went back and forth to the Royal Free. A principal document was finished in the autumn of 1999, naming Wakefield, Pounder, Carmel, Immunospecifics Biotechnologies (IB Ltd), the medical school, Freemedic, an American foundation called Neuro Immuno Therapeutics, and its head, Hugh Fudenberg, an immunologist.

"Royal Free and Immuno entered into the Letter Agreement (as defined in this Agreement)," began a typically meaty clause. "Under its terms Royal Free was to assign to Immuno the intellectual property rights subsisting in the Inventions. In consideration of this assignment Immuno was to pay £10 000 to Royal Free, and was to grant Freemedic an option, over shares representing 10% of Immuno's issued share capital."

All of this went forward between the parties in secret. Another document aimed to gag the school. "RFUCMS and Freemedic agree to maintain all information about IB Ltd, its business plan, fund raising proposals etc provided by IB Ltd . . . as confidential and will not disclose the same to any third party and will restrict access thereto to the Directors and senior personnel."

This latter document was never signed, and strictly therefore of no effect. But University College London (UCL) honoured its spirit, ensuring that the scheme went unreported. And when I was tipped off about Wakefield's business arrangements, the college fought me for three years under the freedom of information act to keep its involvement hidden.

"UCL is coming to the conclusion," the college told the hospital in a February 2005 email, "that many of our docs on file fall into the exemption under section 36 of the Act whereby to disclose information 'would or would be likely to prejudice the free and frank provision of advice; the free and frank exchange of views for the purposes of deliberation or the effective conduct of public affairs.'"

Refusals were authorised by UCL's provost, Malcolm Grant, a professor of environmental law. Only when Richard Thomas, at the time

the UK's information commissioner, travelled to the college's offices and later served a formal notice, did they release the documents into my hands.

Among the more striking were those through which the school could deny any involvement in the scheme. "That is to say if Freemedic choose not to be associated with the company in the first instance they may not wish to exercise their options until they are ready to be associated at some time in the future," Tarhan wrote to child 10's father in July 1999, as they divided the notional spoils. "We have discussed the reasons for this before."

Another letter— to Wakefield— in November 1999 said: "Therefore neither Freemedic nor the School are in any way involved with Carmel until such options are formally exercised and shares are taken up."

Why investors might have paused

But for all the preparations, ready for presentation to investors, one critical issue for the apparent inventions was not broached—that the company's ambitious products might not work.

Investment analysts told me that the late 1990s was a prime time to raise cash from optimists. "Money flowing into the City post-deregulation had driven the start-up of a load of inexperienced investment schemes in biotech," one pointed out. "Very few venture capitalists have the technical knowledge."

Investors might have been encouraged by the mounting vaccine scare and by the *Lancet's* backing for Wakefield.[26] But there were curious fundamentals in the secret scheme which the best informed investors might have noticed.

Firstly, transfer factor, for the proposed treatments and vaccines, had long been abandoned by industry. Proposed in the 1940s as a bespoke blood product remedy, it was all but killed by impractical cost, risk of infection, and lack of evidence or standards. Later reformulated as a treated milk pill, as in proposals such as Wakefield's—which relied on the colostrum of pregnant goats—experts suggest that it is therapeutically inert. Today, it is promoted on the internet as a cure all.

Secondly, there was Hugh Fudenberg, the American immunologist with his Neuro Immuno Therapeutics foundation. He was under sanction at the time from his local medical board over his prescription and use of controlled drugs.[27] When I interviewed him in August 2004 for a Channel 4 documentary,[18] he claimed to cure autism with transfer factor, which he said he rolled out like pizza "three molecules deep" on his North Carolina kitchen table.

"And where does that come from?" I asked.

"From my bone marrow."

"From your own personal bone marrow?"

"Yeah."

Another hidden flaw, which would emerge only later, was the Dublin measles tests—over which vaccine lawsuits in Britain and America would founder. These tests were promoted as detecting persistent virus from past MMR vaccinations. But blood from Walker-Smith's patients, analysed by O'Leary, failed to give consistent results.

"The 1998 *Lancet* research had been a sham. Trying to replicate it with greater numbers would have been hopeless"

For instance, child 2 had all the elements for Wakefield's theory: regressive autism, bowel problems (actually diagnosed as a food intolerance[28]), and a mother who blamed MMR. He was vaccinated at 15 months of age in November 1989. A blood test for the virus 11 years later was negative. Then, two years after that, another result from the boy was positive. Then, two months after that, one was negative.

Preparing for the launch

In advance of such results, Wakefield relied on what he called a series of "impending" papers. "A variety of topics were discussed in the meeting with reference to the forthcoming publication of the paper in *Nature* (date to be confirmed)," said a confidential Carmel "communications programme," for example, passed to me by someone present.

The launch was scheduled for March 2000, with an attention grabbing stunt three months earlier. No *Nature* paper appeared, and Wakefield's platform was to be a London meeting of the Pathological Society of Great Britain and Ireland. There, with O'Leary and Pounder (who both declined to comment on my findings), he planned to present research claiming a breakthrough. Based on alleged gut biopsy samples from Walker-Smith's patients—10 with autism and three with Crohn's disease—tested at the Dublin laboratory, it claimed a "possible causal link"[29] and, given a Wakefield presentation, promised a storm like the press conference two years before.

Meanwhile, he nurtured relationships, with drug industry support, including front of the plane overseas travel. "Please find enclosed a cheque for £2876.70 from Axcan Pharma Inc, a refund of my airfare with regard to my Canadian trip," he told the special trustees, for example, as he put final touches to the scheme. He was also then negotiating a Johnson & Johnson consultancy[30] and had longstanding connections with Merck and SmithKline Beecham.

The scheme unravels

But as the Carmel plans were finalised, Wakefield's fortunes reversed. On the brink of his business launch, it foundered.

The unravelling began after the arrival in the school of a new head of medicine: Mark Pepys. A fellow of the Royal Society and a specialist in amyloid diseases, he brought huge grants and was now the school's biggest name. He was astounded to find Wakefield being feted. "I said I wouldn't transfer my unit if he was there," Pepys told me. "And you know what they did? They promoted him."

With Chris Llewellyn-Smith, a theoretical physicist and at that time UCL's provost, Pepys struck in December 1999, barely two months after starting at the Royal Free. Wakefield was summoned from the hospital's Hampstead campus to the college's central London headquarters. He was challenged over the scheme, then on the verge of fruition, and was given a two page letter.

"We remain concerned about a possible serious conflict of interest between your academic employment by UCL, and your involvement with Carmel," it said, in part. "This concern arose originally because the company's business plan appears to depend on premature, scientifically unjustified publication of results, which do not conform to the rigorous academic and scientific standards that are generally expected."

This marked the end of any commercial deals with Wakefield, and the beginning of his end at the Royal Free. When eventually ousted from his job, he said, "I have been asked to go

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- Feature: Wakefield's "autistic enterocolitis" under the microscope (*BMJ* 2010;340:c1127)
- News: Wakefield is struck off for the "serious and wide-ranging findings against him" (*BMJ* 2010;340:c2803)
- News: *Lancet* retracts Wakefield's MMR paper (*BMJ* 2010;340:c696)
- Observations: After Wakefield—the real questions that need addressing (*BMJ* 2010;340:c2829)
- Observations: Reflections on investigating Wakefield (*BMJ* 2010;340:c672)

because my research results are unpopular."[31] And in response to my investigation, he would allege sinister conspiracies to stop him revealing what he claimed were vaccine secrets.[32 33]

But the paperwork does not show this. Despite all that had happened, UCL volunteered to support his work. It offered him continuation on the staff, or a year's paid absence, to test his MMR theories. He was promised help for a study of 150 children (to try to replicate his *Lancet* claims from just 12) and, in return for withdrawing from the January London conference, he would be given the intellectual property free.

"Good scientific practice," the provost's letter stressed, "now demands that you and others seek to confirm or refute robustly, reliably, and above all reproducibly, the possible causal relationships between MMR vaccination and autism/"autistic enterocolitis"/inflammatory bowel disease that you have postulated."

At the time, Wakefield agreed. Then his employer waited. It prompted, waited longer, and prompted again. "Three months have elapsed," Llewellyn-Smith wrote to him in March 2000, asking for "a progress report on the study proposed" and "not to make any public statements" in the meantime.

But the study did not happen. The 1998 *Lancet* research had been a sham.[10] Trying to replicate it with greater numbers would have been hopeless.

Wakefield, however, shrugged off his noncompliance as arising from some fault of the school's. "It is clear that academic freedom is essential, and cannot be traded," he eventually responded in September 2000. "It is the unanimous decision of my collaborators and co-workers that it is only appropriate that we define our research objectives, we enact the studies as appropriately reviewed and approved, and we decide as and when we deem the work suitable for submission for peer review."

This was a step too far, and in October 2001 Wakefield was shown the door. As I understand it, he got two years' money, a statement clearing him of misconduct, the intellectual property for £10, uncollected, and a gag on Royal Free comment. "We paid him to go away," Pepys told me. "And, of course, one of the conditions of him going away was that I wasn't supposed to say anything critical of him to anybody, for ever after."

Wakefield would never perform the research anywhere, or prove his measles theory. His vaccine plans—predictably—went nowhere. And when I put these matters to him, he and his lawyers acknowledged receipt but offered no further response.

Public fears over the vaccine had yet to reach their peak. My investigation would not begin for two years. But Wakefield would never again hold an academic post, and the secret scheme behind the scare was no more.

Brian Deer journalist, London, UK **briandeer.com**

Funding: Brian Deer's investigation was funded by the *Sunday Times* of London and the Channel 4 television network. Reports by Deer in the *BMJ* were commissioned and paid for by the journal. No other funding was received, apart from legal costs paid to Deer by the Medical Protection Society on behalf of Andrew Wakefield.

Competing interests: The author has completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available from him on request) and declares no financial relationships with any organisation that might have an interest in this work; BD's investigation led to the GMC proceedings referred to in this report, including the charges. He made many submissions of information, but was not a party or witness in the case, nor involved in its conduct.

Provenance and peer review: Commissioned; not externally peer reviewed.

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Cite this as: *BMJ* 2011;342:c5258

Regulating research

Luisa Dillner talks to Michael Rawlins, the man behind the Academy of Medical Sciences' review of medical research governance, about current hurdles in getting clinical trials started and what can be done to improve the process

One word leaps out of the document *A new pathway for the regulation and governance of health research*, the keenly awaited report on research governance from the Academy of Medical Sciences. "It's 'proportionate'," says Michael Rawlins, chairman of the National Institute for Health and Clinical Excellence and of the expert working group that wrote the report. "But I would say there is another word too: symmetry," he adds. He is sitting in the refurbished offices of the academy in Portland Place, London, two days before Christmas while the report, in draft form, is being polished for release.

"These words are very important because the arrangements we have for regulation of trials are disproportionate and asymmetrical," he adds. "They are disproportionate because the degree of risk is assumed to be constant, whereas in reality the degree of risk in trials varies hugely from 'first in man' studies to me giving you an aspirin and then asking you for a blood sample. They are asymmetrical because on the one hand it is quite appropriate for regulatory authorities or ethics committees to decline to approve inappropriate studies, but on the other hand to decline to approve an appropriate study carries the risk of losing the benefits that you could have got from doing the study. Some things are remarkably benign and some things are potentially very risky, but the whole system needs to be designed to take these things into account."

The review was announced by the previous health secretary Andy Burnham in March 2010 and started in May. The academy was asked to review the regulation and governance of medical research in the United Kingdom, concentrating on clinical trials. The academy had already published a report in January 2010, *Reaping the rewards: a vision for UK medical science*, warning that, worldwide, the proportion of clinical trials that were conducted in the UK had fallen from 6% in 2000 to 2% in 2006. This was, the report said, because the regulatory requirements, particularly from the European Union's Clinical Trials Directive, were stifling research in the UK.

The idea of a review seems to have been embraced by the present government, which, in its white paper *Equity and excellence: liberating the NHS* published earlier this year, committed to "consider the legislation affecting medical research, and the bureaucracy that flows from it, and bring forward plans for radical simplification."

"They have been waiting for the academy's review," says Rawlins. "We got a move on. It helped that we had more responses to this than to any other inquiry the academy has ever done. We had more than 300 people write in. They told a very similar story. There was no great divergence of view. The working party itself comprised a disparate group of people—some from academia, some from industry—but you couldn't put a piece of paper between their views."

The new agency would provide a single point of entry for research applications in the UK

The EU Clinical Trials Directive

Respondents to the review cited two main bottlenecks to starting research projects. One was the Clinical Trials Directive, set up in 2001 to protect trial participants, improve ethical standards of trials across the EU, and harmonise the administration of the governance of clinical research. A public consultation on the effects of this legislation in January 2010 found that it had had some negative consequences, such as increased costs and more administrative hurdles in trials. The European Commission has since said it will revise the legislation.

"There is evidence that the directive is burdensome," says Rawlins. "There is also evidence it has damaged academic and clinical trials. The proportion of patients in Europe who are in pharmaceutical trials, which make up 75% of all clinical trials, has fallen by a third. The European Commission said it would do a review a year ago, but now says it does not have enough staff to do anything until 2012."

The directive is felt to be unfair by the research community in the UK because it is not implemented consistently across member states. "In the UK we implement it to the letter," says Rawlins. "The directive is grossly over regulatory."

The problem with consistency arises from the broad definitions in the directive of "clinical trial" and "investigational medicinal products." For example, a trial of a licensed product for an established use in a group of patients who would receive it anyway can be classed as being an interventional clinical trial simply because an investigation such as a brain scan would be carried out to study disease progression.

Rawlins gives the example of a colleague who was studying in children the genes that regulate warfarin metabolism in white blood cells. The children were already on warfarin, but the extra blood sample drawn for the study meant that the trial was classified as being an interventional clinical trial and thus subject to the regulations of the directive. "Inspectors came round and gave him a hard time for not reporting serious unexpected adverse drug reactions, but those rules are for new drugs. For warfarin the adverse effects are known already," says Rawlins. "There are some nonsense things in the directive. In our report we are asking the Medicines and Healthcare Products Regulatory Agency (MHRA) to take a more

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Cutting the research budget (*BMJ* 2010; 341:c5128)

proportionate view of the European directive. There is latitude for them to be proportionate."

Industry finds the directive easier to cope with than the academic community because it can afford to pay for departments to deal with the regulations. However, the MHRA has already recognised the need for risk stratification in clinical trials and, in partnership with the Medical Research Council and the Department of Health, is undertaking a project to look at the management of risk in trials within existing legislation.

The MHRA also performs what are called "good clinical practice inspections" to ensure that researchers doing interventional studies comply with regulatory requirements. The academy heard from some researchers who criticised the behaviour of inspectors, finding them unprofessional and intimidating. "If you're an inspector you may feel you have to be adversarial," he says. "We did hear evidence about the inspections being about ticking boxes."

Managing multiple trusts

The second bottleneck, and the most irksome for many researchers, is obtaining permission from NHS trusts to carry out the research. The report says that current processes are bureaucratic, with duplication and reinterpretation of checks by NHS trusts, inconsistency in those checks (for example, with different rules for accessing patient data), and no clear mechanism for signing off multicentre studies.

Submissions to the academy highlighted the inconsistencies and delays in the permissions process and the difficulties in negotiating contracts and costs to do research. The National Institute for Health Research coordinating system for gaining NHS permissions was cited as having helped to streamline the approval process. The academy's report includes evidence from Kidney Research UK showing that for one trial getting permissions from individual trusts took anything from five to 29 weeks.

"It is a rate limiting step to get approval from all trusts in a study. It requires lots of duplicated effort," says Rawlins. "Also, trusts are risk averse."

A national governing body

Out of the report's 32 recommendations, the one that Rawlins believes will solve the major problems stifling research is the creation of a new agency that will act as a single regulator.

"This health research agency was more than hinted at in the government's white paper," says Rawlins. "The government was minded to set it up but wanted to wait for our report to say what should be in it. We are proposing that the health secretary creates a special health authority as an interim measure for this new health research agency so that we can start the reforms in the report."

The new agency would provide a single point of entry for research applications in the UK (although Rawlins acknowledges that it may not be possible to do this because of differences in legislation in the devolved nations). It would oversee approvals for medical research involving humans, provide a single ethics opinion (subsuming the functions of the National Research Ethics Service), provide specialist approvals and licences, and include a new National Research Governance Service that would streamline and centralise checks on research projects in the NHS. This governance service would replace the current process of multiple checks by individual NHS trusts with study wide checks on the governance of trials. It would also recommend whether research projects are suitable, and introduce timelines for providing NHS permission as well as a costing structure for research studies. Individual trusts would be left to undertake only local checks for feasibility and to report within 20 working days on their willingness to participate in a study. Rawlins cites the success of the National Research Ethics Service in streamlining ethics approval for multicentre trials and talks of the benefits of accessing the rest of the system through one point of contact. "We would like some of the glitter from the NRES [National Research Ethics Service]," he says.

The academy's report stresses the importance of a cultural shift within the NHS: for it to embrace the importance of research in all of its trusts. "We want trust boards to take a much greater interest in the research they're doing," says Rawlins. "We want research directors to be tabled to talk to the board about how their trust is performing in terms of number of patients recruited into trials, number of trials, and, eventually, the number of papers published. We want them not only to take an interest in but to have some pride in their contribution to the growth of knowledge. Trust boards have some responsibility to the patients of the future. Otherwise we'll be standing still all the time."

Rawlins is keen to emphasise that he isn't advocating that research is for everyone. It is equally important to encourage doctors to learn the skills of critical appraisal. "Juniors need to have some idea of what research should influence their practice. They should know the difference between good and bad research," he explains. "Otherwise they will be locked in permafrost for their future practice."

Given that cultural change is notoriously difficult to achieve in the NHS, the academy suggests the importance of research should be visible at the level of the new NHS Commissioning Board. "The director general of research should be on the new commissioning board," says Rawlins. "The board should hear reports of research activities in trusts."

Does Rawlins think his report will upset any of the stakeholders who gave evidence to the review? "Some NHS trusts may feel that research isn't their thing," Rawlins answers readily. "I hope they will get over that defensive reaction and come round to thinking, as I do, that clinical research is good for patients."

The place of research governance

This report is, says Rawlins, who has been chairman of NICE since it was set up in 1999, one of the most important he has been involved in. "When I look back to when I started doing research, there was no regulatory system. We did what we wanted, mostly to each other."

As a junior doctor Rawlins and a colleague brewed up blood cells, mixed in dead bacteria, and infused the solution into each other to induce fevers. He set up his first ethics committee after the dean of Newcastle University Medical School refused to allow him to study the addictive effects of cannabis by trying it himself.

"We objected and said we should have a proper ethics committee," says Rawlins. "So the dean said I could set one up and run it. I have always been a passionate believer in clinical research: it's the best way of finding how disease occurs and new ways to treat it."

Luisa Dillner head of new product development, BMJ, Tavistock Square, London, UK ldillner@bmj.com

Competing interests: LD is a non-executive director for NHS Direct and writes a column in the *Guardian*.
Provenance and peer review: Commissioned; not externally peer reviewed.
Cite this as: *BMJ* 2011;342:c7461

***A new pathway for the regulation and governance of health research*: main recommendations**

- The European Commission should act quickly to revise or amend the EU Clinical Trials Directive
- The Department of Health should establish a new National Research and Governance Service to oversee a streamlined, common process for acquiring research and development permission for all studies in the NHS
- A national Health Research Agency should be established as an arm's length body to oversee the regulation and governance of health research
- This agency should set and deliver standard national timelines for approval of trials