Assuring research integrity in the wake of Wakefield

Not just a bad apple, but a defective barrel

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In a grove of trees in the grounds of the National Academy of Sciences in Washington, DC, is a statue in memory of Albert Einstein. On it are engraved three of his sayings. One reads: "The right to search for truth implies also a duty; one must not conceal any part of what one has recognised to be true."

Science is our best way of knowing. When work presented as science is shown to be corrupt, it not only discredits that work and its authors, but it also discredits science. The series of linked articles by Brian Deer illustrates many of the ways that science can be corrupted.[1-3] Above all, Deer shows that the conventional biomedical research mechanisms intended to assure research integrity completely failed.

Unfortunately, we have been here before. Investigators involved with the 1932 US Public Health Service Tuskegee Syphilis Study deceitfully enrolled subjects with latent syphilis and denied them available treatment for 40 years in order to study the natural course of the disease.[4] As part of a 1963 study to determine the body's ability to reject foreign cells, patients at the Brooklyn Jewish Chronic Disease Hospital were injected with live cancer cells without their knowledge and without oversight from the institution's research committee.[5] From 1944 to 1974, the US government conducted several radiation experiments, some of which involved the use of non-therapeutic radioactive tracers in children and increased their risk of developing cancer.[6] And in 1981, it was discovered that John Darsee, a clinical investigator at Harvard Medical School, had fabricated data in several experiments published in high profile medical journals that ultimately culminated in widespread retractions of his work and a ban from funding from the National Institutes of Health for 10 years.[7] These experiments have since become symbolic of unethical research on human subjects and of scientific misconduct, and there is little doubt that Andrew Wakefield's 1998 study will too.[8]

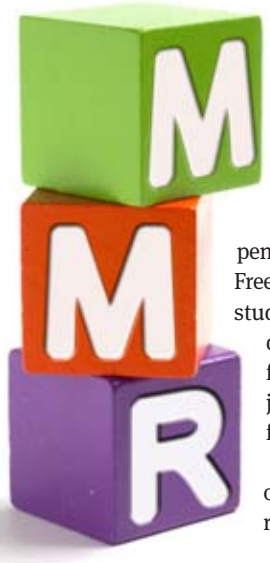
How could this happen again? To answer this, perhaps we need to focus less on the people involved and more on the defects within the biomedical research enterprise that permit such egregious misconduct. After all, Wakefield was able to circumvent the existing safeguards established to ensure the responsible conduct of research, the protection of research subjects, and the accurate and honest publication of research findings.

To begin, we need to frame research incidents like Wakefield's as adverse events, akin to clinical adverse events. Doing so would expose them to the same level of scrutiny that we currently apply to clinical adverse events. The goal would also be the same: prevention of future occurrences by learning from our failures. Prevention of clinical adverse events is one of the cornerstones of healthcare quality improvement and patient safety. Prevention of research adverse events should be no less important for the protection of human subjects, future patients who might receive the wrong treatment as a result of the adverse event, and research integrity.

Investigations into clinical adverse events are focused more on systems of care than on individuals (so called bad apples) for several reasons. Firstly, most adverse events result from flaws in systems of care rather than incompetent or malevolent individuals.[9] Secondly, the bad apple framework connotes punishment and can hinder the disclosure of—and ability to learn from—errors.[10] Thirdly, focusing on individuals' misconduct is likely to yield simplistic answers and premature closure. Lastly, and perhaps most importantly, without fundamentally changing the way work is done, other similarly trained and motivated personnel are prone to repeat the same errors.

Marcia Angell wrote in 1992 that "all those involved in the research enterprise at each step of the process—investigators, IRBs [institutional review boards], funding agencies, reviewers, and editors—have an obligation to evaluate the ethical content of a work just as they evaluate the scientific content."[11]

Deer's articles reveal the urgent need to understand why there was a failure of multiple systems within the research enterprise. Why weren't Wakefield's conflicts of interests recognised and exposed sooner? Why didn't Wakefield's co-investigators recognise or bring attention to the study's methodological flaws? Why wasn't Wakefield's research misconduct and non-compliance with ethics approval recognised by the Royal Free or its ethics committee? Why wasn't there a full, independent investigation by the *Lancet* or the Royal Free when the veracity and quality of Wakefield's study were initially questioned? These are the questions that we need to pursue if we are to fix a system that failed to protect human subjects and the public from the consequences of fraudulent science.



Deer's articles also highlight the existence of a culture and informal customs within the research enterprise that, unless changed, will

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- Feature: How the case against the MMR vaccine was fixed (*BMJ* 2011;342:c5347)
- Editorial: Wakefield's article linking MMR vaccine and autism was fraudulent (*BMJ* 2011;342:c7452)
- Feature: How the vaccine crisis was meant to make money (*BMJ* 2011;342:c5258)

Discuss the credibility of Wakefield's MMR paper on doc2doc, BMJ Group's global online clinical community, at http://bit.ly/dIHKcx

impede needed improvements. "Culture always trumps strategy" (M Bard, personal communication, 2010). Even the most elaborate strategies, procedures, and interventions designed to prevent future research adverse events will be unsuccessful unless problematic aspects of culture and unwritten customs are explored, understood, and tackled.

Let's start now. We must transcend traditional hierarchies and authority gradients to empower everyone in the research enterprise—especially those on the front lines, such as research assistants, data analysts, and project managers—to raise questions and "stop the line."[12] We must train our research leaders—such as department chairs and medical school deans—to manage such inquiries. We must not allow it to be "customary" for journal editors "to discuss and take the word of those against whom the allegations are made."[3] Lastly, when allegations of research misconduct or unethical research are brought to the attention of research leadership, these leaders must recognise that they often have a conflict of interest in managing these allegations. As occurred in the Darsee case, institutions may have an overwhelming drive to keep things internal rather than utilise an independent mechanism—such as an audit by a panel of scientists unaffiliated with the institution—to search for the truth. And as in the Wakefield case, journal editors may find it hard to put aside their own investment in a piece of research that they have decided to publish and defended against post-publication criticism. That it fell to a journalist to expose the extent of the misconduct in Wakefield's research is telling.

Thirteen years later, we are only now beginning to understand the root causes of the multiple system failures involved in the Wakefield incident. We must strengthen our ability to investigate research adverse events. We need to use the tools and techniques available to protect the safety of patients in the clinical realm to protect research subjects. We also need to rethink and reform our customs and culture. The disastrous impact that Wakefield's study has had on vaccine coverage, recrudescence of disease, public trust, and, most of all, science, requires that we do so in haste.

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Regulation and governance of clinical research in the UK

New report aims to remove unnecessary burdens and bureaucracy

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The recent growth in bureaucracy associated with clinical research in the United Kingdom has been a classic example of the law of unintended consequences. The regulatory framework, which has evolved in a piecemeal and uncoordinated fashion over the years, requires the proposed study to undergo a range of assessments (approvals, authorisations, or permissions) by diverse local or national bodies, who generally implement their processes without adjusting for risk. As a result, the regulatory processes are slow, costly, and disincentivising. Measures that were designed to protect patients and improve the quality of UK clinical research have unintentionally placed burdens on commercial and publicly funded studies that result in the studies being conducted less efficiently, or not at all. Between 2000 and 2006, the proportion of patients recruited from the UK to the world's commercial clinical trials fell from 6% to 2%.[1]

In recognition of these problems, the UK government invited the Academy of Medical Sciences to conduct a review of the regulation and governance of clinical research in the UK. The report of the review's working group, chaired by Sir Michael Rawlins, was published on 11 January.[2]

There is widespread recognition of, and frustration with, this unsatisfactory situation. The National Institute for Health Research (NIHR) has implemented several initiatives to reduce bureaucracy, including plans to support more efficient operation of research ethics committees and a coordinated process to streamline permission for clinical research studies from NHS organisations.[3 4] These and other initiatives have brought

Principles that should underpin a regulatory and governance framework

- Safeguard the wellbeing of research participants
- Facilitate high quality clinical research in the public interest
- Be proportionate, efficient, coordinated, and streamlined
- Maintain and build confidence in the conduct and relevance of clinical research through transparency, clarity, accountability, and consistency

Sir Michael Rawlins

incremental benefits, and the establishment of the NIHR Clinical Research Network in England and similar initiatives in the UK devolved administrations represented a substantial investment in an infrastructure to support efficiency and quality in clinical research. Indeed, in England, the numbers of patients recruited to clinical studies more than doubled in a two year period—from 208 200 in 2007-8 to 454 138 in 2009-10. In the North West Exemplar Programme, a project that aimed to show, through active management of certain exemplar studies, that the NHS could support the conduct of commercial clinical trials, the median time to obtain NHS permission to conduct studies at individual sites fell from 98 days to 53 days. Seven of 20 studies recruited the first patient in the world from an exemplar site.[5]

The Academy of Medical Sciences' report makes 17 recommendations, which are based on four principles that should underpin the UK's future regulation and governance framework (box).[2] The key recommendation is the formation of a new health research agency, with two main functions—to streamline all the current arrangements for ethical approval and to provide a national research governance service. Thus, the agency would not only assume responsibility for the national research ethics service, but also specialist ethical approvals and licences. By undertaking all study-wide research governance checks, such a national research governance service would eliminate inefficiency and ensure consistency across study sites. These checks would include review of the arrangements for indemnity and processing of Criminal Records Bureau checks on the principal investigator and other research staff. This would leave individual trusts to focus on assessment of local research feasibility and to confirm their capacity to conduct the study within an agreed time frame.

The report also recognises that further initiatives beyond the Health Research Agency and outside the UK will be needed. Most importantly, many of the unintended consequences have been blamed on the European Clinical Trials Directive and its rigorous implementation by the Medicines and Healthcare products Regulatory Agency. The European Commission is planning a revision of the directive, and the report urges that the revised directive should take into account the proportionality of each study's risk. Similarly, the legislative framework, which relates to access to and use of patient data in clinical research, is complex. The report calls for a thorough review of both the UK's Data Protection Act in relation to health research and the EU Data Directive. The Caldicott guardian is a senior person in each trust who has responsibility for protecting the confidentiality of patient identifiable information and for enabling information to be shared. The report outlines the need for Caldicott guardians to avoid making further requests before approval for those setting up research studies and to focus on facilitating the performance of research studies. It calls for clear guidance to make it clear that researchers should be considered part of a clinical care team and therefore able to access patient information so that they can decide if patients are eligible for recruitment to a clinical study.

The report devotes a whole chapter to how the culture that supports clinical research in the UK can be more positive and promote the attitude that good research is good for patients. It makes several recommendations to help embed research as a core function in the NHS. There are outstanding opportunities in the UK for discoveries from medical research to translate efficiently into clinical applications that would benefit patients. The combination of research excellence from some of the best universities in the world and a large and well organised healthcare system provides a strategic advantage that is widely acknowledged. Recognition of this by NIHR and similar initiatives in the UK devolved administrations has led to the establishment of a research infrastructure within the NHS to support clinical studies for the benefit of patients. The designation of several academic health science centres and systems in the UK is further evidence of the intention to span discovery and translation sciences and provide integrated health delivery and improve global health. It is hoped that, if the recommendations of this report are implemented, better regulation and governance processes will facilitate UK clinical research, while continuing to provide the oversight needed to protect patients and the public to the highest possible degree.

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The life imprisonment of Dr Binayak Sen

This misconceived application of state power requires international action

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Last month a district court of the state of Chattisgarh in central India sentenced Dr Binayak Sen, Indian paediatrician, public health practitioner, and human rights activist, to life imprisonment in a maximum security cell. He was pronounced guilty of sedition and conspiracy against the state.[1] This harsh sentence is particularly paradoxical because Sen was recently recognised by the same state as a respected figure in health and social planning, and last year he was given the Jonathan Mann Award for Health and Human Rights from the Global Health Council.

His crime according to the judgment was being a collaborator for the underground Maoist movement that is active in the newly created state of Chattisgarh, which has a large indigenous (Adivasi) population, an abundance of forests and natural resources, but economic and health deprivation.

Sen, a community physician, and his wife Ilina are known for their work in primary healthcare among mine workers and indigenous communities. Sen's commitment to tackling the deeper social determinants of health has now brought him into conflict with the state. Moving beyond the biomedical and clinical model of healthcare,[2] Sen began to deal with deprived living conditions, poor education in children, and alcoholism, and he found it impossible to disassociate these from the need for community empowerment, political accountability, and ownership of natural resources. He documented the levels of starvation in the state,[3] and as an active member of the People's Union for Civil Liberties he participated in fact finding missions on violations of rights by state forces and systems, including a state sponsored armed people's militia. He provided medical and legal assistance to people who were undergoing trial, including alleged militants, always under supervision of the state authorities. This made him a ready target for accusation of conspiracy by the state, which recently armed itself with an antiterrorist law that goes far beyond the national act. Sen, who has been a critic of both Maoist and state violence now finds himself convicted under a section of the penal code that was used by the British in colonial times to convict Gandhi.[4]

The recent judgment has received worldwide condemnation. Global voices have included statements by Nobel laureates Noam Chomsky and Amartya Sen,[5] Amnesty International,[6] the Global Health Council,[7] Human Rights Watch, and Physicians for Human Rights, and other commentators.[4 8] At a national level, an upsurge of solidarity has included meetings and vigils in all the major cities of India and statements by eminent jurists, professionals, and activists.

Although the state has attempted to portray him as dangerous, Sen is following in the footsteps of generations of social physicians. Like Virchow in an earlier century, others in more recent years, and charters of health movements,[9] he focuses on the social, economic, and political roots of ill health. Recent prescriptions from the World Health Organization on primary healthcare and the social determinants of health have strengthened action towards equity, rights, and social determinants of health, just the areas that Sen focused on.[10 11]

This misconceived and vindictive application of state power requires international action. Professional societies in India have an opportunity to reflect on the larger social and political role of doctors and to express their support for Sen. Supporters in other countries could urge their government to apply diplomatic pressure towards justice for Sen and call for a review of Indian laws on sedition, which have lent themselves to such abuse.

In today's economically driven society, commerce drives international relations. Foreign direct investment in India is often in mining industries in states such as Chattisgarh, which have rich natural resources. Ultimately, such investment comes from shareholders. Better awareness of how shareholders' money may drive state policies to the detriment of the disadvantaged could redirect investment towards more ethical and equitable projects, especially where funds belong to charitable or philanthropic institutions.

Finally the implications for those who are tackling the social determinants of health must be considered, and we need to enhance our collective voice against all instances where doctors and health workers are targeted by ruling elites and vested interests.

It is ironic that one of Sen's last public appearances before his incarceration was at the release of a book that was a critique of current medical practice and new paradigms of action.[12] Notably, in an expeditious response, the joint Committee on Human Rights of the US National Academy of Sciences, National Academy of Engineering, and Institute of Medicine has expressed its reservations about the conviction of Sen and its hope for his "full exoneration" (personal communication from the chairperson of the committee, 2011).

BINAYAK SEN BY STRDEL/AFP/GETTY

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Civil rights groups decry conviction of Indian paediatrician who pioneered community health (*BMJ* 2010;341:c7438)

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The new *BMJ* series on therapeutics

Will discuss how to prescribe effectively and safely

SUNG-IL KIM/CORBIS

PRACTICE, p 224

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Which drug to choose? As doctors, we all try to keep our patients' needs, values, and expectations uppermost in decision making, as other parties jostle to influence our prescribing choices. Guideline bodies issue advice; authorities warn of cost; pharmaceutical companies ply us with their wares; new studies may throw accepted practice into doubt. Responding to its readers' call for practical, evidence based advice, the *BMJ* is launching a new therapeutics series. Its last concerted foray into this field was a series called "New Drugs," which ended in the 1990s. The new series will mostly cover drug classes used to treat common conditions and serious conditions with high morbidity or mortality, especially new drugs and old drugs with important new indications or about which controversy exists.

Rational prescribing—that is, safe, effective, and cost effective prescribing—still requires evaluation of the potential benefits of treatment, ensuring that these outweigh any likely harm, and wherever possible tailoring the treatment to the individual patient.[1] This is the essence of the discipline of clinical pharmacology and therapeutics. An individual patient may be denied optimal benefits of treatment by poor prescribing: underprescribing (the failure to give a medicine whose likely benefits greatly exceed the risk of harm); overprescribing (the unwarranted prescription of a medicine whose risk of harm exceeds its likely benefit, overall or relative to another medicine); or misprescribing (prescribing the wrong medicine).[2]

Since the days of the previous *BMJ* series on therapeutics, we have all become much more aware of "opportunity cost" (when resources spent providing a sometimes small benefit for one group of patients deprives another group of patients of treatments that may be more clinically effective and cost effective). In the United Kingdom, the National Institute for Health and Clinical Excellence, the Scottish Medicines Consortium, and the All Wales Medicines Strategy Group advise on decision making in relation to this.[3] We are even more aware of the harms that can accompany prescribing.[4] Adverse drug reactions may account for 6.5% of all acute medical admissions to hospital.[5]

The use of data in clinical practice has become more sophisticated. The "number needed to treat" arrived in 1988,[6] and "evidence based medicine" was first described in 1992.[7] Since then, evidence based medicine with its focus on systematic evaluation of systematically gathered evidence has largely replaced opinion. This can make prescribing decisions easier. However, a gap exists between clinical trials and the real world of clinical practice. The data showing that about half of all the patients prescribed antihypertensive treatment had stopped taking it within one year should give pause for thought.[8]

The *BMJ*'s new series will therefore not only synthesise the data on benefits and harms but also discuss cost effectiveness, briefly offer comparisons with other drug classes where relevant, and include guidance on how to advise patients, encourage adherence, and monitor for effectiveness and harm. It will explore the evolution of newer drugs (such as the newer antipsychotic agents) and their merits and demerits in clinical practice.

A greater appreciation of the prevalence of venous thromboembolism and the value of evidence based guidance has highlighted the importance of using prophylaxis against deep vein thrombosis,[9] and the first article in the new series concerns new oral anticoagulants for this indication.[10] The shifting prevalence of some diseases has partly driven other changes. For example, the rise in type 2 diabetes, combined with changes in practice, has increased the use of insulin in non-insulin dependent disease and of new anti-diabetic agents—both subjects of future articles in the series.

The *BMJ* hopes this series will help readers to navigate therapeutic choices, and in time it plans to expand it to include non-drug therapeutic interventions such as devices and procedures.

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The *BMJ* is on the iPad

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The *BMJ* is now available as an iPad application (app) for Apple's tablet computer—the first one of its kind to be launched by a general medical journal. The app combines the content chosen for the weekly *BMJ* print journal plus live feeds of news, blogs, podcasts, and videos on bmj.com.

Our aim in developing the app was to deliver a new version of the *BMJ* to the growing number of iPad users worldwide, and to respond to the findings of our online survey of visitors to bmj.com last year. Many international website subscribers who responded to the survey were interested in the print journal, despite not receiving it. We hope the app gives people a sense of what the print *BMJ* looks like each week without lapsing into what usability expert Jakob Neilson described as an "overly strong print metaphor" when he reviewed the iPad after its US launch in April 2010.[1]

Each issue of the app sits behind an image of that week's print cover with clickable cover lines and a colour coded table of contents, including editor's choice, letters, obituaries, views and reviews, and research papers in the same shortened "pico" format that we use for the print journal.

As with other apps, the content displays in both portrait and landscape formats. You can tap images, tables, and graphics so that they expand to be viewed in more detail. Each article includes clickable links to authors' email addresses, plus related blogs, podcasts, and relevant articles from the archive. There is also a response link to bmj.com, which enables you to comment on articles.

The app has distinct channels—one for journal articles and others for user generated blogs, podcasts, and videos. As in the print and online *BMJ*, the articles comprise research, education, and scholarly comment such as editorials and analysis, followed by the journalistic content—features, reviews, and opinion. Journal articles swipe from left to right. Content on the news, blogs, video, and podcast channels scrolls up and down. Because these are live feeds, they update each time the iPad connects to the internet.

We decided to give news its own channel because stories are posted twice a day online and only a selection appears in print. The iPad app offers the opportunity to present news as it is published and to include all stories, not just the selection chosen each week for print.

The iPad is an ideal device to display our growing library of educational and research based video content. Individual films are embedded in relevant articles and also presented in a separate channel (as they are on bmj.com). We took a similar approach with the *BMJ* weekly podcast, which is also available via iTunes. We are now looking to adapt the *BMJ* for other mobile devices—those that use Google's Android operating system and Amazon's Kindle e-reader, plus Sony's eReader and Blackberry. But we are confident that the iPad was the most appropriate device on which to launch the *BMJ*'s first app, with its long battery life and touch interface. The device's large colour screen is well suited to the complex layouts of some of our journal articles. Its portability as a tablet computer means it is actively being talked about as a point of care tool for busy doctors in both primary and secondary care settings. Scholarly Kitchen blogger Kent Anderson referred to it recently as "a real workhorse in hospital information systems."[2]

In a *BMJ Careers* article on the iPad and medicine, Ian Robertson and Edward Miles directly mention the device's capacity for storing textbooks and journals.[3] However, they point out that the backlit display can cause eye strain if used for long periods. Because of this we have used the print versions of most articles. The full length versions can still be accessed on bmj.com.

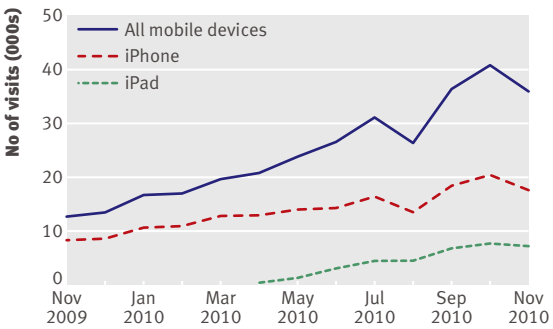
The iPad does have its detractors. In his review for the *New York Times*, David Pogue said he had never seen a product polarise opinion so much.[4] Disliked by "techies," he described its fans as "regular people" and the device itself as a "good goof-proof computer for technophobes, the aged and the young."

Perhaps the figures speak for themselves. More than two million iPads were sold in April and May 2010,[2] and Apple's 2010 fourth quarter results, ending September 25, recorded 4.19 million iPad sales.[5]

The volume of iPad sales is reflected in visitor statistics to BMJ Group products. Increasing numbers of readers are accessing our content from mobile devices. In October 2010, of the 40 812 visits from mobile devices, 7803 were from the iPad (figure). We now have dedicated iPhone apps for *BMJ Careers* and *Student BMJ*. Thousands of people have downloaded our two decision support iPhone apps, *Best Practice* and *Differential Diagnosis*.

After an editorial in May this year welcoming the iPad's imminent arrival,[6] many readers volunteered to road test the new *BMJ* app. We will be seeking their feedback in the coming weeks, and we are already thinking about version 2. Please give us your views and suggestions for enhancements, either in rapid responses or on the Apple store.

Review the iPad version of *BMJ* on doc2doc, BMJ Group's global online clinical community, at http://bit.ly/ih7LSb



Visits to the *BMJ* by various types of mobile device

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