Missing clinical trial data
A threat to the integrity of evidence based medicine

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Clinical medicine involves making decisions under uncertainty. Clinical research aims to reduce this uncertainty, usually by performing experiments on groups of people who consent to run the risks of such trials in the belief that the resulting knowledge will benefit others. Most clinicians assume that the complex regulatory systems that govern human research ensure that this knowledge is relevant, reliable, and properly disseminated. It generally comes as a shock to clinicians, and certainly to the public, to learn that this is far from the case.

The linked cluster of papers on unpublished evidence should reinforce this sense of shock. These articles confirm the fact that a large proportion of evidence from human trials is unreported, and much of what is reported is done so inadequately. We are not dealing here with trial design, hidden bias, or problems of data analysis—we are talking simply about the absence of the data. And this is no academic matter, because missing data about harm in trials can harm patients, and incomplete data about benefit can lead to futile costs to health systems. Moreover, researchers or others who deliberately conceal trial results have breached their ethical duty to trial participants.

The linked articles look closely at the extent, causes, and consequences of unpublished evidence from clinical trials. Hart and colleagues incorporated unpublished evidence into existing meta-analyses of nine drugs approved by the US Food and Drug Administration in 2001 and 2002.1 These reanalyses produced identical estimates of drug efficacy in just three of 41 cases (7%); in the remaining cases, estimates of drug efficacy were evenly split between more (19/41) and less (19/41). It is sometimes assumed that incorporation of missing data will reduce estimates of drug benefits, but this study shows that “publication bias” can cut both ways. Each increment of data can change the overall picture, but in most cases with no certainty that the picture is complete.

A fundamental step towards tackling this problem was taken in 2005, when, as Chan describes in the Research Methods and Reporting section, prior registration of all trials became a condition for later publication.2 Chan details the ways in which authors of systematic reviews can search for unpublished evidence, and he strikes an optimistic note when he states that “Key stakeholders—including medical journal editors, legislators, and funding agencies—provide enforcement mechanisms that have greatly improved adherence to registration practices.” However, two studies we publish give little cause for optimism that this adherence extends to timely sharing of trial results. A survey of publicly funded research in the United States between 2005 and 2008 by Ross and colleagues shows that registration is not followed by reporting of summary results within 30 months of completion in more than half of trials.3 Even at three years, one third remain unpublished. The US Food and Drug Administration Amendments Act of 2007 made publication of a results summary on ClinicalTrials.gov within 12 months mandatory for all eligible trials in the US “initiated or ongoing as of September 2007”—Prayle and colleagues examine the extent to which this has happened.4 The tally stands at 22%. When the word “mandatory” turns out to mandate so little, the need for stronger mechanisms of enforcement becomes very clear.

Most clinical interventions in current use, however, are based on trials carried out before the era of mandatory registration, and here the task of data retrieval by systematic reviewers and national advisory bodies becomes impossible. Wieseler and colleagues show that the different documents available to researchers and regulators—internally produced study reports, study findings published in peer reviewed journals, and results posted in results registries—supplement each other, but that reporting quality is highest in study reports. However, the effort required to find and collate these sources can be prodigious and seldom guarantees completeness.5 In their just published Cochrane review update on antiviral treatments for influenza, Jefferson and colleagues describe a painstaking search for information from undisclosed trials stretching over several years.6

There is an “Alice in Wonderland” feel to these investigators’ efforts—acting on the public’s behalf, searching over hill and dale and among the paperwork of regulatory bodies and drug companies to put together pieces of data that should have been freely available in the first place. Even when data on individual participants are made available, they form only part of the jigsaw, and Ahmed and colleagues describe the problems of fitting in such data when the whole picture is not known.7

Finally, to find the randomised clinical trials that have been published in the medical literature, nearly every student, clinician, or researcher turns first to Medline among the biomedical databases. But Wieland and colleagues find that many reports of randomised controlled trials entered into Medline between 2006 and 2011 have not been indexed as such; thus, simply entering the search term “randomised controlled trial” into this database will miss many of these...
trials, despite the best efforts of the Cochrane Collaboration and the US National Library of Medicine.8

What is clear from the linked studies is that past failures to ensure proper regulation and registration of clinical trials, and a current culture of haphazard publication and incomplete data disclosure, make the proper analysis of the harms and benefits of common interventions almost impossible for systematic reviewers. Our patients will have to live with the consequences of these failures for many years to come. Retrospective disclosure of full individual participant data would be an important first step towards better understanding of the benefits and harms of many kinds of treatment. A model for this is provided by Medtronic’s recent agreement to release full individual participant data relating to its controversial bone product—recombinant human bone morphogenetic protein-2—to independent analysis teams; so there is no longer any convincing reason for other companies to refuse similar disclosure of de-identified participant data from all past trials.9

The main challenge is to ensure better systems for the future. Because “the optimal systematic review would have complete information about every trial—the full protocol, final study report, raw dataset, and any journal publications and regulatory submissions,”2 10 a prosy system of research governance should insist on nothing less. This may require the global organisation of a suitable shared database for all raw data from human trials—an obvious next step for the World Health Organization after its excellent work on the International Clinical Trials Registry Platform Search Portal. Concealment of data should be regarded as the serious ethical breach that it is, and clinical researchers who fail to disclose data should be subject to disciplinary action by professional organisations. This may achieve quicker results than legislation in individual countries, although this is also desirable. These changes have been long called for,11 and delay has already caused harm. The evidence we publish shows that the current situation is a disservice to research participants, patients, health systems, and the whole endeavour of clinical medicine.

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11 Chalmers I. Underreporting research is scientific misconduct. JAMA 1990;263:1405-8.

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Research misconduct in the UK

Time to act

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Research misconduct can harm patients, distort the evidence base, misdirect research effort, waste funds, and damage public trust in science. Countries all over the developed world are now recognising the need to set up systems to deter, detect, and investigate research misconduct. Why does the United Kingdom have no plans to do the same?

As Aniket Tavare outlines in the linked feature,1 high profile cases of misconduct have led the United States, Canada, Sweden, Norway, and Poland, among others, to create formal mechanisms for overseeing research integrity. In most countries responsibility lies with the institutions, but oversight varies greatly, and it is unclear which systems are most effective and efficient. None is perfect—the remit of the US Office of Research Integrity is limited to publicly funded health research; Australia’s recently established Research Integrity Committee is already being criticised for lacking teeth. But each system shows that the problem has been acknowledged, that institutions accept primary responsibility, and that governments and funders are seriously committed to tackling misconduct openly and with a range of statutory powers.

In contrast, the UK has no official national body. The UK Research Integrity Office was established in 2006 and has done some useful things. But its function has always been advisory, and now that the major funders represented by Research Councils UK (RCUK) have decided not to continue the funding, it relies on voluntary funding from institutions. The Research Integrity Futures Working Group, set up by RCUK and Universities UK (UUK) and other bodies, has also apparently come to nothing. The working group’s report commissioned in 2009 called for an independent advisory body, similar to the UK Research Integrity Office but operating across all research sectors and with a stronger monitoring and preventive function.2 But RCUK pleaded budget cuts and decided not to implement the recommendations.3 It says it is working with UUK on a “concordat” to take some aspects forward, but two years on nothing has been announced.4

This lack of concerted action is succoured by a prevailing view within the UK’s research establishment that we don’t have a problem; that a major global scandal like Wakefield’s research into the measles, mumps, and rubella vaccine (MMR) and autism, hosted by the UK, is a one off in terms both of the research misconduct and the institution’s failure to investigate promptly and properly. Such things are extremely rare we are told, and institutions around the country are doing fine. In a letter to the BMJ, Alan Langlands, chairman of the Higher Education Funding Council for England (HEFCE), which provides infrastructure funding for universities, said: “HEFCE funded institutions are aware...
that they should report any instance where they believe that high standards of rigour have not been met. In these circumstances they must take account of reputational damage to their institution and the wider UK research base and we would expect them to conduct a thorough investigation. Bearing in mind that cases of significant, proven research misconduct are very rare, we consider that these arrangements are sufficient and proportionate.”

However, there are enough known or emerging cases to suggest that the UK’s apparent shortage of publicly investigated examples has more to do with a closed, competitive, and fearful academic culture than with Britain’s researchers being uniquely honest. MMR may indeed be an extreme example, but it is not an isolated case.\(^6\) \(^7\) Reports from the UK and elsewhere show that institutions are failing to investigate adequately, if at all.\(^8\) In some cases, mishandling of misconduct allegations has devastated the careers of honest researchers.\(^9\) In others, fraudulent research or unscientific behaviour goes unquestioned for years. Sometimes the researcher is allowed to continue in another capacity, as happened in Sheffield,\(^1\) or to make an “honourable” exit, as Wakefield did when he was quietly sacked in 2001.\(^10\) Sometimes a confidentiality clause prevents publicity. The lack of openness certainly prevents learning.

Although institutions are generally best placed to conduct inquiries, and they have duties as employers for supervision and discipline, many will not know how to go about a proper investigation. Institutions also have an inherent conflict of interest. They must compete for funding and commercial advantage as never before and may be tempted to avoid investiga- tion of misconduct allegations to suggest that the UK’s apparent shortage of publicly investigated examples has more to do with a closed, competitive, and fearful academic culture than with Britain’s researchers being uniquely honest. MMR may indeed be an extreme example, but it is not an isolated case.\(^6\) \(^7\) Reports from the UK and elsewhere show that institutions are failing to investigate adequately, if at all.\(^8\) In some cases, mishandling of misconduct allegations has devastated the careers of honest researchers.\(^9\) In others, fraudulent research or unscientific behaviour goes unquestioned for years. Sometimes the researcher is allowed to continue in another capacity, as happened in Sheffield,\(^1\) or to make an “honourable” exit, as Wakefield did when he was quietly sacked in 2001.\(^10\) Sometimes a confidentiality clause prevents publicity. The lack of openness certainly prevents learning.

Although institutions are generally best placed to conduct inquiries, and they have duties as employers for supervision and discipline, many will not know how to go about a proper investigation. Institutions also have an inherent conflict of interest. They must compete for funding and commercial advantage as never before and may be tempted to avoid investigating or to sweep findings under the carpet to protect their reputation or avert a legal challenge. The need for a formal body to conduct research misconduct inquiries is therefore long overdue.

This week we will be sending a brief survey to all the BMJ’s UK based authors and reviewers, asking them whether they have witnessed or had first-hand knowledge of UK based scientists or doctors inappropriately adjusting, excluding, altering, or fabricating data, and whether they are aware of any cases of possible research misconduct at their institution that, in their view, have not been properly investigated. We will present the results at a high level meeting on research misconduct in the UK on 12 January.

The meeting will hear that research misconduct is alive and well in the UK even when tightly defined as intentional acts of falsification and fabrication. It is almost certainly flourishing when defined more broadly—as some are now arguing it should be\(^12\)—to include a wide range of questionable behaviours that threaten the integrity of science, including suppression of data and failure to publish research results.

The meeting will also hear from speakers in Sweden, Germany, the Netherlands, and the US, and then from representatives of UK funders and institutions on how they see their role in dealing with the problem. Solutions already being aired in advance of the meeting are in line with recommendations from the House of Commons select committee inquiry into peer review: that all institutions should appoint a research integrity officer.\(^3\) Provided these people are sufficiently senior, they could function like the Caldicott guardians now established at each NHS trust, who are responsible for protecting the integrity of patient data. As well as overseeing routine monitoring, they would be someone in authority to whom people could take their concerns in confidence. Funders could make it a prerequisite for funding that institutions appoint such a person and openly investigate potential misconduct. The new Health Research Authority, or a beefed up version of UK Research Integrity Office, could provide independent statutory oversight to make sure they do things right and publish their findings. Such an arrangement need not be overly expensive or bureaucratic.

Concerns about research misconduct in the UK are not new. The two previous editors of the BMJ made repeated efforts to galvanise the research community into action. Reading their editorials brings an uneasy sense of déjà vœ.\(^11\)\(^14\) UK science and medicine deserve better. Doing nothing is not an option.

Competing interests. All authors have completed the ICMJE uniformly formatted disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; both the BMJ and the Committee on Publication Ethics (COPE) are committed to improving the integrity of research; the BMJ is a founding member of COPE; EW is on the advisory board for the UK Research Integrity Office (this is an unpaid position) and runs training courses for researchers, editors, writers, and publishers that sometimes cover publication ethics; she has also received expenses from various organisations for speaking on publication ethics. Provenance and peer review. Commissioned; externally peer reviewed.

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10. Dyer B. How the vaccine crisis was meant to make money. BMJ 2011;342:c2528.


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Feature, p 23
The NHS in England in 2012

A year in which the medical profession must exercise leadership on quality and safety

Chris Ham

Three issues have dominated debate about health policy in England during 2011. The first has been the Health and Social Care Bill currently before parliament, which seems likely to pass into law in the spring. Amendments made after the report of the Future Forum have done little to appease critics, who continue to worry that the bill marks a major step towards privatising aspects of NHS provision and commissioning.

The second issue is the performance of the NHS. With funding unlikely to increase by more than a fraction of 1% in real terms over the next six years, there are widespread concerns that patient care will be affected as financial deficits increase. At a time when several NHS organisations are struggling to balance their budgets and even more are not meeting targets on waiting times and other key priorities, the auguries are not promising.

The third concern is the quality of patient care. Here, there is an apparent contradiction between reports from the Commonwealth Fund and the Organisation for Economic Co-operation and Development, which show the NHS in a positive light, and evidence from the Care Quality Commission of the inability of some organisations to treat older patients with dignity and respect. The Francis Inquiry into the Mid Staffordshire NHS Foundation Trust has trained the spotlight on failures of quality in one hospital, and the inquiry’s report—expected during the first half of 2012—is likely to contain wide ranging recommendations designed to prevent these failures being repeated.

The Francis Inquiry has focused on how the commissioning, supervisory, and regulatory bodies detect and correct deficiencies in service provision. In the course of taking evidence, the inquiry heard about the part played by professional regulators, the Department of Health, the strategic health authority, the primary care trust, the Healthcare Commission, Monitor, and the leadership of the Mid Staffordshire NHS Foundation Trust itself. One of the recurring themes has been the complexity of relationships between these bodies and the challenges they face in identifying and preventing quality failures in hospitals.

In his summing up at the end of the inquiry’s hearings, Robert Francis listed 20 areas on which he expects to come to conclusions and make recommendations. These areas include the interface between the regulation of governance, finance, and quality and safety standards; the use of commissioning to require and monitor safety and quality standards; and the means of embedding the patient voice throughout the system. Particular emphasis was placed on recruitment, training, and regulation of staff, including the senior managers of NHS organisations, and the exercise of the fitness to practise functions of professional regulatory bodies.

All three of the issues that have dominated debate in 2011 will remain important in 2012, although the performance of the NHS and the quality of patient care will become more prominent. This is because the funding pressures facing NHS organisations are bound to increase, which will make it difficult to sustain the improvements in performance seen in the past decade, and also because the inquiry’s report will be a big event. The failure to provide an acceptable standard of care to patients will rightly attract a great deal of interest, and it may lead to the government introducing new legislation.

Yet if the report of the Francis Inquiry makes uncomfortable reading for regulators, managers, and non-executive board members, it will throw down serious challenges to doctors and other clinicians. However well designed the arrangements for regulating performance and managing services may be, the quality and safety of patient care depend first and foremost on the skills of the clinical teams delivering that care. Failures such as those that tragically occurred at Mid Staffordshire raise fundamental questions about the doctors, nurses, and other front line staff working at the hospital, and why they did not act sooner or more decisively to prevent quality failures happening.

Bruce Keogh, medical director for the NHS in England, emphasised this point in his evidence to the Francis Inquiry, arguing that the first area on which to focus is the quality of individual clinicians and their professionalism. He went on to contend that this needed to be supplemented by peer surveillance within clinical teams and a willingness to challenge poor practice and performance. Also important was the support available to teams and the role of senior leaders within hospitals in enabling clinicians to deliver the best possible care. It might be added that doctors also have a responsibility to challenge failures in care by their peers and other clinicians—even when they may be subject to so called gagging clauses—as do nurses, midwives, and other regulated professionals.

All of this suggests that the royal colleges, the General Medical Council, and other institutions with a role in ensuring high standards of clinical practice will find themselves under scrutiny as the role of professionalism returns centre stage. As a consequence, renewed attention will be given to revalidation and appraisal and to ways in which clinical leadership in hospitals and other organisations providing care can be strengthened. The caution here is that the failures in paediatric heart surgery at Bristol Royal Infirmary in the 1990s occurred in a hospital led by a medical chief executive, suggesting that simply putting doctors in charge is unlikely to be sufficient.

The opportunity for the medical profession in this context is to demonstrate a degree of collective leadership that in the past has been difficult to mobilise. If part of the solution to the problems of Mid Staffordshire is to develop a new professionalism, then it behoves the institutions with an interest in this area to overcome their differences and show the public and government that they are willing to take a lead on patient quality and safety. If they are able to rise to this challenge, the leaders of the profession can become players on the pitch rather than remaining, as so often, spectators and commentators on the sidelines. Competing interests: None declared.

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