Fraud and deceit in medical research

Fraud and deceit in medical research is a serious issue that may be more prevalent than currently thought. This article examines the extent and history of medical research fraud and looks at the current and future mechanisms for detection and prevention.

Deceit in scientific research is important as it damages the reputation of, and undermines public support for, science. Despite this, a survey of scientists published in *Nature* found that about one third of respondents admitted to some aspect of research misconduct (Martinson et al, 2005). Fraud in medical research is especially significant as it distorts our knowledge base with potential adverse effects for patients. If public confidence is to be maintained, the integrity, probity and trustworthiness of scientific and medical researchers are essential. Around £6 billion of UK taxpayers' money is annually spent on research. It follows that fraud should be dealt with on the highest levels by fair, competent and transparent processes. Despite numerous scandals highlighting the scale of the problem, the UK has been slow to recognize and deal with medical research fraud and lags behind many western countries with regards to this issue.

The extent of the problem

In the UK, the Joint Consensus Conference on Misconduct in Biomedical Research in 1999 defined misconduct as being 'behaviour by a researcher, intentional or not, that falls short of good ethical and scientific standards' (Royal College of Physicians of Edinburgh, 2000). This definition is quite vague and although it includes more subtle methods of dishonesty it may also encompass genuine errors in study design that could not be considered to be misconduct. The Committee of Publication Ethics (COPE) defines misconduct as 'intention to cause others to regard as true, that which is not true'. This is a broader definition and also includes the fact that misconduct may be perpetrated by authors, referees or institutions.

Researcher-derived misconduct includes: non-publication of results, authorship without contribution, lack of adequate control experiments, omitting data not conforming to the hypothesis, misquoting authors, manipulating statistical methods and data invention. Referee or institution misconduct involves: rejecting papers which do not agree with their theories, rejecting funding for work which may contradict work which the individual or institution may have an interest in and rejection of papers with non-significant results. One other form of deceit includes false 'whistle blowing'. This is often perpetrated by high-level scientists with the aim of discrediting the work of others as even after allegations are proved false, a level of suspicion usually remains.

Why do researchers deviate from an acceptable moral framework?

There is increasing pressure placed upon junior and senior doctors to publish. Research output is often used as a yardstick of ability and career progression is generally dependent upon the number of publications. Discretionary points are also often awarded on the basis of research produced so creating a financial incentive after becoming a consultant. This direct financial reward as in any sphere of life may be a powerful motivator for an individual to falsify data in order to produce results. There is no consensus or evidence, however, as to the motivation of dishonest doctors. Indeed it has been suggested that a large amount of fraud is perpetrated by people with a 'Messianic complex' (Medawar, 1967) and the desire to do good.

It must be remembered that the award of a medical degree does not confer any higher moral statute to the individual. It follows that there will be a proportion of doctors who are dishonest. Competition and money are likely to be the two main driving forces but laziness, desire for fame, greed and an inability to tell right from wrong may also contribute (Rennie, 1998).

History of fraud in medical research

In order to understand the importance of the subject, a few notable incidences are now discussed. These cases highlight specific aspects of the history of medical research misconduct and help us understand the subject more clearly.

Case studies

One of the most notorious cases is that of Dr Summerlin from New York (Lock, 2001). In 1974 this researcher faked results of a transplantation procedure. He darkened transplanted skin patches in white mice with a felt tip pen and alleged human corneas had been transplanted into rabbits. The deceit was discovered at a demonstration of the results. Of note, the repercussions give an insight into the prevailing attitude of the time. It was believed that Dr Summerlin was unduly stressed, and as such was treated by an enforced period of leave on full pay, as opposed to professional sanctions.

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In 1975 a GP, Dr Singh, was found to have falsified clinical trial forms which led to his results differing significantly from other test sources (Lock, 2001). He was reported to the General Medical Council by the pharmaceutical company and had his name removed from the register. This case was important as it encouraged the feeling that fraud was motivated by financial greed and perpetrated by doctors not regularly involved in research.

Dr Darsee, a cardiologist, was found to have falsified experimental results by a research assistant in 1981 (Brunwald, 1992). It was felt that this was an isolated case and as such, his boss allowed him to keep his job although his contract was not renewed. He was still involved in ongoing projects when it became apparent that the deliberate fabrication of results was endemic in his work. It appeared that the explanation of the isolated incident from stressed doctors might paint a misleading picture of fraud in medical research with some doctors being simply dishonest. Many salient points were highlighted including the need for suspicion of authors producing very high volumes of publications in short spaces of time, co-authorship from heads of departments who have had no input into the paper and a lack of supervision of junior trainees. Journal inadequacies were also highlighted including a subsequent lack of retractions for misleading articles, inadequacy and limitations of peer review, and the difficulty in getting repeated work published. The Darsee episode brought research fraud in the USA to light and was integral in the recognition that a central body was required to investigate allegations of misconduct.

Sir Cyril Burt, a leading psychologist, developed the idea that IQ was hereditary as opposed to environmental. He studied monozygotic and dizygotic twins reared separately. Subsequent to his death, many detractors emerged and claimed his research was fraudulent. This was picked up by the media and became accepted by the scientific community. It took years for it to be shown that there was no basis to these claims (Joynson, 1989). This example highlights the problems of false whistle blowing.

In 1995 Dr Pearce, a gynaecology consultant from St George's Hospital in London, brought medical fraud in the UK to light. He falsified a case report purporting to the successful transplantation of an ectopic embryo into the uterus. There was no evidence that this had ever occurred. He was later found to have falsified results concerning research on polycystic ovaries in a paper that was published in a journal where Dr Pearce was an editor, as was his boss who was listed as a co-author on the paper. This case was well publicized but was only one of a number of cases from the UK involving doctors from teaching hospitals. Dr Anderton, a physician from Edinburgh (Mitchell, 1997), falsified results in a drug trial, as did Professor Davies from St Bartholomew's Hospital (Dyer, 1999). These demonstrated that the problem was more widespread than thought by many. These cases were important as they sparked concerns that medical fraud was more widespread in the UK than was previously thought and initiated a response from leading medical editors. They relayed their concern through editorials in leading journals and this led to the formation of COPE.

Pharmaceutical-sponsored research

The public perceives that the pharmaceutical industry has lower ethical standards than the general medical community. Continual stories of ethically corrupt practices in the marketing of products does not paint the industry in a favourable light (Moynihan, 2005). There are incidences of bribery (Bosch, 1999), 'ghost authorship' abuses (Eaton, 2005) and statistical impropriety. The altruistic aims of research are to scientifically demonstrate the validity of a null hypothesis. Pharmaceutical companies fund research with a specific aim of increasing product sales. There may therefore be a conscious or subconscious bias inherent to the research. Indeed there is evidence that bias is more common in industry-sponsored research (Hong and Bero, 2002; Chalmers and Matthews, 2006).

Pharmaceutical companies are under tremendous financial pressures to reduce costs and increase profits. This pressure can be transmitted to research divisions to cut corners, so hastening the development of new drugs, and to obtain favourable results within clinical trials. Doctors are offered financial rewards to recruit patients for trials and this has led to falsification of data; however, fraud may occur at all levels from medical directors to trial monitors.

The pharmaceutical industry through the Association of the British Pharmaceutical Industry (ABPI) has accepted standards for the conduct of medical research. Globally, the Good Clinical Practice guidelines (International Conference on Harmonisation, 1996) have been adopted under the International Conference on Harmonisation Process (European Commission, 1991) and take precedence in the USA, Europe and Japan. There is no set standard for dealing with fraud and misconduct but a practical policy has been adopted by the industry to reduce fraud. Industry has realized the need for a central regulatory agency which can investigate problems and identify misbehaving doctors across several companies. This recognition may be the result of the potential financial implications of needing to repeat trials and the adverse publicity involved with being associated with fraudulent research. A company may lose millions of pounds if a clinical study needs to be repeated.

Practical measures that have been recommended include publishing strict company guidelines in order to nurture a climate of honesty. Prevention of fraud can be assisted by monitoring trial units more closely and examining returned trial materials and diary cards from patients. Despite this, there is a history of putting profits above patients. One example is the allegations levelled at Merck regarding the cardiovascular risks of rofecoxib (Vioxx). Scientists at Merck were asked to alter manuscripts to reduce the negative implications of their concerns regarding the drug. Subsequently Vioxx was found to increase the risk of cardiovascular events (Krumholz et al, 2007).

Statistics in research

Data may be manipulated or falsified. Data manipulation, when it occurs, is usually performed to achieve statistical significance for a desired result with the intention of achieving publication of the research. Data invention is often performed for financial gain where patients are invented to increase remuneration for testing a product.

Journal editors must shoulder responsibility for putting pressure on researchers to achieve significant results, as the general perception is that non-significant results will not be published. This also directly produces problems caused by publication bias leading to skewed meta-analysis of published data, with emphasis only on positive results.

Statistical methods are used to distinguish genuine rather than random differences between different study groups. The crucial features of the groups and data are:

1. Magnitude of effect of the product on individuals
2. Variability of individuals within any group
3. Number of individuals within a group.

To achieve maximal statistical significance 1 and 3 need to be high and 2 low. This feature is reduced when performing 'equivalence trials' with the aim of demonstrating no differences between treatment groups and control groups. It is used in the pharmaceutical industry when high patient variability is introduced into a trial so differences in side effects between drugs do not achieve significance.

It has also been noted that there are some characteristics of fraudulent research that are identifiable. There are often larger differences between groups with lower variability between groups. Invented data also may show little variation, possess an absence of outliers, demonstrate digit preference and show patterns of digits in the data sets. Statistical methods which are available to evaluate the integrity of data provide clues that misconduct may be taking place and so may indicate the necessity for further investigation.

The UK situation

There are various institutions that are responsible for attempting to regulate medical research in the UK. Ultimately under corporate governance rules, it is the employers who are responsible for investigating and policing research misconduct. In the medical community this responsibility generally falls to NHS trusts and universities.

Committee of Publication Ethics

COPE was convened in 1997 as a reaction from several medical editors who found near insurmountable problems with initiating their own investigations into research fraud. The last published meeting report was from 2003. It identifies that the NHS and universities share corporate responsibilities to monitor and investigate misconduct among their employees. The suggestion is that this can be performed through routine and random monitoring, audit, reporting and whistle blowing. COPE appears to exist for dissemination of ideas at the present time and is unable to implement policy. They have published guidelines on good clinical practice and are calling for a financed, independent regulatory body to be convened, which can investigate alleged cases of misconduct. They recommend following the example of the Scandinavians and the Americans who have admitted that there is a problem and are trying to rectify it.

Despite this, there are still calls for greater sanctions against perpetrators of fraud. In 2004, an editorial in *Nature* called for greater sanctions from universities and journals (Anonymous, 2004). The case of Asim Kurjak, a professor from Croatia, provides one example of plagiarism can become widespread. He was found in 1979 to have plagiarized an article from a journal yet he escaped proper censure and 15 years later submitted a student's PhD thesis as his own work (Chalmers, 2006).

The General Medical Council

From 2000–2003, 16 cases of misconduct were investigated by the General Medical Council (O'Brian, 2003). These included misappropriating funds, failure to follow protocols, forging signatures of co-authors and patients, falsifying data and failure to obtain consent. The General Medical Council have stated that their remit is to take action where a doctor is not fit to practice. This means they will not investigate more minor cases of misconduct.

Ethics committees

The role of the ethics committee is to encourage good quality, well-justified, well-planned and appropriately designed biomedical research. They should work to ensure only robust well-designed projects are commenced, which through their design make it difficult for fraud to flourish and prevents bad research practice.

The future

Montesquteu's triad states that it is vital to keep the legislative, judiciary and executive separate. Currently NHS institutions and universities set up ad-hoc committees to deal with problems. These panels investigate, judge and punish, so mixing all three levels. This process may work well, such as when performed by the Dean of St George's Hospital for the Pearce scandal, but all too often it is cumbersome and offers no protection to whistle blowers.

It is important to realize that any process should be transparent and fair to all parties involved, be they the accused or accuser. There are also obvious limitations to this system, for example in cases where doctors who perpetrated the misconduct no longer working for the institution.

At the 2003 COPE meeting the General Medical Council proposed a joint working group be formed to take investigations of allegations from employers to an independent group – a ‘council for research integrity’. This should be the way forward as it solves in part most of the above problems.

Conclusions

The incidence of medical research misconduct may be far more prevalent than is currently assumed. The UK first needs to recognize the gravity of the problem before it can address it. Many of the Royal Colleges have argued that the issue of fraud is caused by a lack of integrity on an individual basis and as such needs to be dealt with on a local level. Thus the responsibility lies with institutions for ensuring that processes are in place to encourage more honest working practices. This is a valid point but is only part of the solution. Much of Europe and the USA has already found efficient ways in which national or regional bodies have been established to investigate research fraud. It took the Darsee scandal in the USA to motivate Al Gore to campaign for the creation of the Office of Research Integrity in the USA. Despite numerous scandals in the UK, however, there does not appear to be much movement in implementing the recommendations from COPE or indeed those of the Royal College of Physicians of Edinburgh (Royal College of Physicians of Edinburgh, 2000). Until this occurs the UK will continue to lag behind much of the western world in dealing with this issue. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Deceit in scientific research is important as it damages the reputation of, and undermines public support for science.
- Misconduct may be perpetrated by authors, referees or institutions.
- There is increasing pressure placed upon junior and senior doctors to publish.
- The explanation of the isolated incident from stressed doctors may paint a misleading picture of fraud in medical research with some doctors being simply dishonest.
- Data may be manipulated or falsified. Data manipulation, when it occurs, is usually performed to achieve statistical significance for a desired result with the intention of achieving publication of the research.
- The Committee of Publication Ethics was convened in 1998 as a reaction from several medical editors who found near insurmountable problems with initiating their own investigations into research fraud.
- The role of the ethics committee is to encourage good quality, well-justified, well-planned and appropriately designed biomedical research.
- The UK first needs to recognize the gravity of the problem before it can address it.