PERSPECTIVE

Tackling Conflict of Interest and Misconduct in Biomedical Research

JP DADHICH
From Breastfeeding Promotion Network of India (BPNI)
Correspondence to: Dr JP Dadhich, 23, Canara Apartments, Sector 13, Rohini, Delhi 110085, India. jpdadhich@bpni.org

Biomedical research forms the basis of evidence based practices in the field of health and nutrition. However, it is, increasingly being seen that conflicts of interest and misconduct are undermining research. More and more instances of using research to promote commercial interest are being reported. Fraudulent means, in the quest to publish, are also being used. This article discusses conflict of interest and misconduct in bio-medical research, reviews scientific evidence available on the subject, and proposes some solutions to check the menace.

Each year, hundreds of biomedical journals across the world publish innumerable research papers. Based on this research, clinical guidelines are prepared to guide experts, governments and implementing agencies. Biomedical research also feeds the judicious use of current best evidence in making patient care decisions [1,2]. Notwithstanding the importance of the biomedical research, it is imperative that it remains impartial, free from fraud, misconduct and conflict of interest.

Conflict of interest: (COI) in the biomedical research is defined as "a set of conditions in which professional judgment concerning a primary interest (such as patients' welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain)" [3].

Financial conflict of interest is a condition and not a behaviour and therefore, circumstances determine presence or absence of conflict of interest [3,4]. The International Committee of Medical Journal Editors (ICMJE) form for disclosure of potential conflicts of interest requires information from the researchers about the work under consideration for publication like receiving grant, consulting fee or honorarium, payment for writing or reviewing the manuscript etc.; and information about the relevant financial activities outside the submitted work including board membership, consultancy, payment for lectures including service on speakers bureaus [5].

It is worth noting that academic–industry relationships have been an essential component of research enterprise in the life sciences. Empirical data show that more than half of academic scientists have such relationships, which most often involve consulting, receiving research funding, and providing scientific advice [6]. Whether the scenario is similar in India, is difficult to judge from the literature.

Fraudulent research includes fabrication, falsification or modification of data or results. Research misconduct, which may be detrimental to patients, also damage public trust in science [7]. In a survey of more than 2700 researchers, one in seven UK based scientists or doctors had witnessed colleagues' intentionally altering or fabricating data during their research or for the purposes of publication [8].

Various agencies have outlined ethical codes of conduct to carry out and report research [9]. The question is, can vested interests manipulate these norms to their own advantage rather than for the public good? Can there be a bias in favour of those who are funding the research? Can guideline developing bodies be affected by unrecognised extraneous interests? This article is an attempt to explore some of these issues.

ANATOMY OF RESEARCH FUNDING - WHO IS SETTING AGENDA FOR THE BIOMEDICAL RESEARCH?

To understand the issue of COI and misconduct in biomedical research, it is important to explore the anatomy of research funding. Worldwide about $56bn [(£37.3bn) per year was spent on health research by both the public and private sectors [10]. The Global Forum for Health Research estimated a decade ago that less than 10% of research funds were spent on the diseases that account for 90% of the global burden of disease. The funding of research studies by the industry, with explicit or implicit conflict of interest has been a growing trend. A recent review concluded that author conflict of interest in psychiatric clinical trials was associated with a greater likelihood of reporting a drug to be superior to placebo [11].

A study, which analyzed research papers published in

New England Journal of Medicine and Journal of American Medical Association, found that private corporations funded approximately one third of original manuscripts published in these journals [12]. The study also found that around 30% articles had one or more authors with a conflict of interest. Interestingly, authors with conflicting interest were 10 to 20 times less likely to present negative findings than those without COI. The fact that negative findings were less commonly reported by the authors having COI raises serious ethical questions [12]. Since such research is conducted in collaboration with prestigious researchers, institutes and even government agencies, very few questions are probably asked even by the editors.

Another issue with far-reaching implications is the choice of topics and the direction of research. A survey of over 1,200 faculty members at 40 major US universities about research activities and funding revealed that commercial considerations have at one time or other influenced their choice of research projects [13].

In spite of the widespread concerns about the conflict of interest in research, some researchers do not find it troublesome and felt that it is a lot of fuss about nothing [14]. An editor of a journal, dismissed objections about the infant formula companies sponsoring research in the field of infant nutrition, saying that people who are raising such objections have scanty scientific-epidemiological evidence, together with a most unwelcome emotional component [14]. One researcher, whose many studies were sponsored by the formula industry, has stressed for a close collaboration between responsible clinical scientists and industry as research in infant nutrition requires substantial investment [16].

These arguments are now becoming steadily less tenable as evidence accumulates on the influence of conflict of interest [14]. As per Rundall [17], "Companies - especially those that are the subject of criticism - have a particular need to offer sponsorship, knowing that it works on many levels. Without it, companies find it much harder to silence potential critics; create the image that they are responsible "corporate citizens" who can be trusted to regulate themselves; influence public health policies and priorities; link their name to prestigious non-governmental organisations, United Nations agencies, and health professionals; affect the direction and outcome of research; create dependency; and create public confusion about the real causes of poverty" [17].

DISCLOSURE OF FUNDING FROM INDUSTRY

To address the great variability in the processes that different journals use to ask about and report authors' potential conflicts of interest, the International Committee of Medical Journal Editors [ICMJE] developed an electronic uniform disclosure form in 2009, which was piloted by ICMJE member journals [5] and since than being used by many international scientific journals. Such modalities, even if diligently adhered to; ultimately leave the onus of judging the veracity of the research findings on the reader, who may sometimes fail to take note of the conflict of interest. An analysis of conflict of interest policies of medical journals has revealed that most journals' COI definitions were limited to direct financial interests only and there was a discrepancy between journals having COI policies (89%) and those requiring signed statements (54%) from each author [18].

A study to look at information on ethics reporting and authorship in the "instructions to authors" section of 59 Indian medical journals found that guidance regarding ethics was mentioned in 43 (72.8%) journals; and authorship criteria were mentioned in 38 (64.5%) journals [19]. Authorship criteria according to the International Committee of Medical Journal Editors were mentioned only in 35 (59.3%) journals and guidance regarding contributors' details was mentioned only in 30 (50.8%) journals [19]. These findings suggest that in spite of so much concern about the issue of conflict of interest in the reported research, not many journals in India enforce strict criteria for authors to include ethical requirements. A survey of 221 North American medical journal editors also found that only 26% required authors to reveal their funding sources [20] and in a large number of pharmacoeconomic studies funding sources are not specified [21]. Two older studies also report similar data from the US [19,20]. It is also often seen that ties between researchers and industry are omitted from media reports about drugs [22].

MISCONDUCT IN CLINICAL TRIALS

Health and nutrition industry including drug and infant formula companies have been able to create a scientific environment which helps them to promote their products to the unsuspecting consumers. They are being knowingly or unknowingly getting support from researchers, funding agencies and scientific journals. There is an inherent conflict of interest in such collaborations, where the company strives to advance its interests by controlling the scientific agenda and focusing on product development [23].

Motivated and fraudulent research

There are examples of misconduct by researchers in the conducting of research or reporting of results. There are

instances, when both false results and conclusions were reported or some important negative facts were suppressed. Some examples are given below.

In 2005, the journal *Nutrition* retracted a paper by a Canadian researcher about effect of vitamin and trace-element supplementation on cognitive function in elderly subjects [24], as the author failed to give an adequate response to the questions asked by the journal about the research findings [25]. The research claimed to be a randomized double blind placebo controlled trial concluded that physiological amounts of vitamins and trace elements could improve cognitive function in elderly people. This paper had been initially submitted to the *British Medical Journal*, which had rejected it due to doubts about the paper [26]. In fact, one of the reviewers had opined that the paper "had all the hallmarks of having been entirely invented" [26]. Apart from having concerns related to the veracity of the data, the author also held a patent for the nutritional supplement that was claimed to improve cognition, thus, clearly reflecting a COI. Further to this, the Canadian Broadcasting Corporation investigated the past research works of the scientist and found that he indulged in fraudulent research on hypoallergenic formula also. His research studies, which were supported by the formula manufacturers (Nestle, Mead Johnson), concluded that the products were hypoallergenic [27]. It is important to note here that armed with the 'scientific evidence' provided by the 'research' mentioned above, one of the company which sponsored the research, promoted its' product among the public for years to create a market for the product and convince medical professionals with claims about protection against allergy [28].

One more example of manipulated research is studies on the anti-hyperglycemic drug Rosiglitazone. After being in use for many years, research suggested that Rosiglitazone carried cardiovascular risks [29,30]. A post-marketing surveillance funded by the manufacturer of the drug (GlaxoSmithKline plc UK), concluded that addition of rosiglitazone to glucose-lowering therapy in people with type 2 diabetes is confirmed to increase the risk of heart failure [31]. The United States Senate Committee on Finance, suggested that excess cardiovascular events with the drug appeared as early as 2004, but that the manufacturer, GlaxoSmithKline (GSK), intimidated researchers and manipulated the scientific process for commercial advantage [32,33]. Further, a systematic review on rosiglitazone and the risk of myocardial infarction found that articles that gave a favorable view on the risks were significantly more likely to have authors with financial ties to the manufacturers of anti-hyperglycemic agents in general, and rosiglitazone in particular, than those with unfavorable views [34].

Ghost writing and guest authorship

Guest authorship is the practice of publishing studies prepared by hired medical writers but signed by academic "guest authors" who are invited to add their names without fulfilling authorship criteria. Sometimes, "guest authorship" is accompanied by "ghostwriting," which occurs when a published article fails to acknowledge the original writer or writers' contributions. Ghostwriting of medical journal articles raises serious ethical and legal concerns, bearing on the integrity of medical research and scientific evidence used in legal disputes [35].It has been reported that clinical trial manuscripts related to a drug were authored by sponsor employees but first authorship was attributed to academically affiliated investigators who did not always disclose industry financial support. Similar authorship patterns had happened in the review manuscripts [36].

CONFLICT OF INTEREST IN DRAFTING POLICIES AND CLINICAL GUIDELINES

Research findings are ultimately used to formulate policies and clinical guidelines. Potential conflict of interest due to involvement of scientists and researchers with financial ties with industry in global and local policy making is a major issue. COIs can arise through authors having financial links with industry, including being paid consultancies or honoraria, or holding company shares [37]. During the recent pandemic flu, investigations revealed that key scientists advising the World Health Organization on planning for an influenza pandemic had done paid work for pharmaceutical firms that stood to gain from the guidance they wrote. These conflicts of interest have never been publicly disclosed by WHO [38].

Similarly, a study of 313 Australian clinical guidelines used between 2003 and 2007 found that only 15% of guidelines on the National Health and Medical Research Council portal from the most prolific developers have published conflict of interest statements, and fewer detail the processes used to manage conflicts [39]. A cross sectional study to determine the prevalence of financial conflict of interest among members of panels to develop clinical guidelines for diabetes and hyperlipidemia found that out of 288 panel members, 52% had had conflicts [37]. Interestingly, it was revealed that panel members from government sponsored guidelines were less likely to have conflicts of interest compared with guidelines sponsored by non-government sources [40].

Review articles are widely used to draft policies and formulate guidelines. It has been shown that the

BOX I INTERVENTIONS SUGGESTED AS A SAFEGUARD AGAINST MISCONDUCT IN BIOMEDICAL RESEARCH

1. *Public funding of the biomedical research:* Public funding for the basic and core health issues, including intervention operational studies, according to the needs of the country should be enhanced and made available to agencies without any conflict of interest.
2. *Regulatory system for financial support and publications of research:* To improve the system to effectively regulate and oversee researchers and journals and to improve the current financial disclosures regulations, we need to enforce a system to regulate financing of the biomedical research studies and publication of research articles. Search engines like PubMed should adopt a mechanism to highlight conflict of interests also with the abstracts and summaries.
3. *Trial Registry:* The issue of selective reporting of the positive and suitable results could be tackled with establishment of trial registry at national and international level. It also helps in bringing a balance to the available evidence by making available both negative as well as positive results. At international level, the WHO International Clinical Trials Registry Platform (ICTRP) has been established [42]. In India, The Clinical Trials Registry- India (CTRI) has been established by the ICMR. The Drugs Controller General (India) has made it mandatory for all the drug trials being conducted in India to get registered with CTRI [43].
4. *Careful scrutiny of scientific studies quoted for the health claims by the industry:* Regulatory provisions should be in place to examine the health claims and the supporting research for a nutritional or pharmaceutical product by the industry.
5. *Effective code of conduct for guidelines and policy panels:* All the experts participating in the guidelines and policy panels should submit a COI statement, which should be published alongwith the guidelines.
6. *Definitive punitive action for misconduct in research and fraudulent research:* Regulatory bodies for clinical research and Academic institutions should have a protocol in place for appropriate action for research misconduct.

conclusions of review articles are strongly associated with the affiliations of their authors. Of 106 reviews on the health effects of passive smoking, 37% (39/106) concluded that passive smoking is not harmful to health; 74% (29/39) of these were written by authors with tobacco industry affiliations. In multiple logistic regression analyses controlling for article quality, peer review status, article topic, and year of publication, the only factor associated with concluding that passive smoking is not harmful was whether an author was affiliated with the tobacco industry [41].

CONCLUSIONS

Biomedical research is crucial to practice evidence based medicine. Hence, it is essential to keep it's sanctity maintained [***Box* I**]. It is evident that scientific tools like biomedical research may be used by the market forces as a medium to gain profits. Medical professionals, policy makers, UN agencies and media should observe due diligence while using research conclusions for public health recommendations, keeping in view the conflict of interest on part of the authors. At the same time, there is a need to find some mechanism in the editing process by the journals to identify the conflict of interest and to notify it to the readers in a more explicit manner.

Funding: None; *Competing interests:* None stated.

REFERENCES

1. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ. 1996; 312:71-2.
2. Evidence-Based Medicine Working Group. Evidence-based medicine. A new approach to teaching the practice of medicine. JAMA. 1992; 268:2420-5.
3. Thompson DF. Understanding financial conflicts of interest. N Engl J Med. 1993; 329:573-6.
4. Kassirer JP, Angell M. Financial conflicts of interest in biomedical research. N Engl J Med. 1993; 329:570-1.
5. International Committee of Medical Journal Editors [ICMJE]. Uniform requirements for manuscripts submitted to biomedical journals. Available at: http://www.icmje.org/coi_disclosure.pdf. Accessed on April 25, 2012.
6. Campbell EG, Zinner DE. Disclosing industry relationships—toward an improved federal research policy. N Engl J Med. 2010; 363:604-6.
7. Godlee F, Wager E. Research misconduct in the UK. BMJ. 2012; 344:d8357.
8. Tavare A. Managing research misconduct: is anyone getting it right? BMJ. 2011; 343:d8212.
9. Indian Council of Medical Research (2006). Ethical guidelines for Biomedical Research on Human subjects. Available at: http://icmr.nic.in/ethical_guidelines.pdf. Accessed on April 30, 2012.
10. Lee K, Mills A. Strengthening governance for global health research. BMJ. 2000; 321:775-6.
11. Perlis RH, Perlis CS, Wu Y, Hwang C, Joseph M, Nierenberg AA. Industry sponsorship and financial conflict of interest in the reporting of clinical trials in psychiatry. Am J Psychiatry. 2005; 162:1957-60.
12. Friedman LS, Richter ED. Relationship between conflicts of interest and research results. J Gen Intern Med. 2004; 19:51-6.
13. Blumenthal D, Gluck M, Louis KS, Stoto MA, Wise D. University-industry research relationships in biotechnology: implications for the university. Science. 1986; 232:1361-6.
14. Smith R. Beyond conflict of interest. Transparency is the

key. BMJ. 1998; 317:291-2.
15. Falkner F. Editorial. Int Child Health. 1997; viii:1.
16. Lucas A. Collaborative research with infant formula companies should not always be censored. BMJ. 1998; 317:333-9.
17. Rundall P. How much research in infant feeding comes from unethical marketing? BMJ. 1998; 317:333-9.
18. Blum JA, Freeman K, Dart RC, Cooper RJ. Requirements and definitions in conflict of interest policies of medical journals. JAMA. 2009; 302:2230-4.
19. Jaykaran, Yadav P, Chavda N, Kantharia ND. Survey of "instructions to authors" of Indian medical journals for reporting of ethics and authorship criteria. Indian J Med Ethics. 2011; 8:36-8.
20. Wilkes MS, Kravitz RL. Policies, practices, and attitudes of North American medical journal editors. J Gen Intern Med. 1995; 10:443-50.
21. Sacristán JA, Bolaños E, Hernández JM, Soto J, Galende I. Publication bias in health economic studies. Pharmacoeconomics. 1997; 11:289-92.
22. Moynihan R, Bero L, Ross-Degnan D, Henry D, Lee K, Watkins J, *et al*. Coverage by the news media of the benefits and risks of medications. N Engl J Med. 2000;342:1645-50.
23. Lo B. Serving two masters - Conflicts of interest in academic medicine. N Engl J Med. 2010;362:669-71.
24. Chandra RK. Effect of vitamin and trace-element supplementation on cognitive function in elderly subjects. Nutrition. 2001;17:709-12.
25. Meguid MM. Retraction of Chandra RK. Effect of vitamin and trace-element supplementation on cognitive function in elderly subjects.(In- Nutrition. 2001;17:709-12); Nutrition 2005;21:286.
26. Smith R. Investigating the previous studies of a fraudulent author. BMJ. 2005;331:288-91.
27. Hamblin T. The secret life of Dr Chandra. BMJ. 2006;332:369.
28. INFACT Canada. Nestlé Scientist's False Claims Exposed. Available at: http://www.infactcanada.ca/Chandra_Feb72006.htm. Accessed on April 25, 2012.
29. Cohen D. Rosiglitazone: what went wrong? BMJ. 2010;341:c4848.
30. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007;356:2457-71.
31. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, *et al*. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes [RECORD]: a multicentre, randomised, open-label trial. Lancet. 2009;373:2125-35.
32. The United States Senate Committee on Finance. Grassley, Baucus release committee report on Avandia. Available at: http://finance.senate.gov/newsroom/chairman/release/?id=bc56b552-efc5-4706-968d-f7032d5cd2e4. Accessed on April 25, 2012.
33. Editorial. Strengthening the credibility of clinical research. Lancet. 2010;375:1225.
34. Wang AT, McCoy CP, Murad MH, Montori VM. Association between industry affiliation and position on cardiovascular risk with rosiglitazone: cross sectional systematic review. BMJ. 2010;340:c1344.
35. Stern S, Lemmens T. Legal remedies for medical ghost writing: imposing fraud liability on guest authors of ghost written articles. PLoS Med. 2010;8:e1001070. Epub 2011 Aug 2.
36. Ross JS, Hill KP, Egilman DS, Krumholz HM. Guest authorship and ghost writing in publications related to rofecoxib: a case study of industry documents from rofecoxib litigation. JAMA. 2008;299:1800-12.
37. Williams MJ, Kevat DA, Loff B. Conflict of interest guidelines for clinical guidelines. Med J Aust. 2011;95:442-5.
38. Cohen D, Carter P. Conflicts of interest. WHO and the pandemic flu "conspiracies". BMJ. 2010;340:c2912.
39. Williams MJ, Kevat DA, Loff B. Conflict of interest guidelines for clinical guidelines. Med J Aust. 2011;195:442-5.
40. Neuman J, Korenstein D, Ross JS, Keyhani S. Prevalence of financial conflicts of interest among panel members producing clinical practice guidelines in Canada and United States: cross sectional study. BMJ. 2011;343:d5621.
41. Barnes DE, Bero LA. Why review articles on the health effects of passive smoking reach different conclusions. JAMA. 1998;279:1566-70.
42. WHO. International Clinical Trials Registry Platform [ICTRP]. Available at: http://www.who.int/ictrp/child/en/. Accessed on March 21, 2012.
43. National Institute of Medical Statistics [NIMS]. The Clinical Trials Registry-India [CTRI]. Available at: http://ctri.nic.in/Clinicaltrials/cont1.php. Accessed on March 21, 2012.