Pitfalls in the publication of scientific literature: a road map to manage conflict of interest and other ethical challenges

Clinical article

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The process of publishing scientific research can be hampered by potential pitfalls for journals and researchers alike; the definition and determination of authorship, legal documentation, data accuracy, and disclosure of financial conflicts of interest are all examples. In the current article, the authors discuss the challenges related to scientific medical writing and provide updated recommendations for both the prevention and management of these issues.

(DOI: 10.3171/2010.8.JNS091834)

Key Words • conflict of interest • ethics • scientific publication • financial disclosure

The publication of scientific literature has come under increasing scrutiny, which has typically been related to several potential pitfalls, including the lack of a clear definition and determination of authorship, incomplete legal and regulatory documentation, uncertain data accuracy, and poorly managed financial COIs. The adverse effects of these pitfalls have brought the traditional processes of scientific inquiry, peer review, and publication into question. Growing public and governmental awareness of these concerns has sparked a number of responses from both authors and journals that have been inconsistent and open to criticism. The purpose of this article is to discuss these challenges to scientific writing and publication. Moreover, various solutions will be presented to assist in the management and prevention of these types of incidents. It is our hope that educating the scientific community about these issues and elucidating the avenues by which they can be addressed will strengthen the quality and reputation of the published literature.

A Hypothetical Scenario

A prominent clinical researcher submits a manuscript detailing the outcomes of a new medical device. As required, the researcher and all coauthors submit signed documentation disclosing all financial relationships including those related to the investigational device. The article undergoes peer review and is accepted for publication.

Shortly after publishing the article, the journal editors are contacted by both the individuals and the institutions involved with the study. The coinvestigators voice concerns over the accuracy of the data presented in the final paper. The academic institution of the principal investigator notes that the published financial COIs do not concord with their internal records. They state that the maker of the new medical device provided financial support in excess of that reported in the journal.

What are the next most appropriate steps to address these concerns? Are there means by which events like this can be prevented?

Background

While the presented scenario is uncommon, a number of highly publicized cases have recently brought this issue to the forefront of both scientific and public attention. Two articles in the orthopedic literature, dealing with either new devices or new pharmaceuticals, have recently been withdrawn because of data fabrication.10,13,17,21 A number of articles touting the benefits of a hormone replacement therapy have been shown to be written not by the listed authors but by paid writers financed by a pharmaceutical company.23 A study reporting the benefits of antidepressant treatment after stroke is called into question over an undisclosed COI between the lead author and the pharmaceutical company.18
These instances bring into question the ethics and motives of the involved parties. They also create an atmosphere of distrust between scientists and the general public. They tarnish the collegiality of academic medicine and call into question the honor code by which we perform and report scientific data. They disrupt the relationship between physicians and patients, making future research endeavors increasingly difficult, hampering innovation. They erode public confidence in scientists, the scientific process, and scientific literature by suggesting impropriety. They offer salacious opportunities for the lay press to decry the rampant corruption in health care and the untoward influence of money on medicine. Lastly, but most ominously, they draw the attention and scrutiny of the government and politicians, eager to safeguard medical care.

Nonetheless, these instances also provide great insight into the more subtle and pervasive influences that COIs can have on scientific work. Our community of clinician-scientists needs to openly scrutinize these occurrences and develop solutions to address and prevent these possible conflicts in scientific publications. If we are unable to do so, the inherent value of the work that we do may be debased and our academic freedom to self-regulate will be taken.

**Potential Pitfalls**

There are many issues that can arise through the publication of a scientific manuscript. The definition and determination of authorship and the order of authorship, the submission of complete and appropriate legal documentation, insurance of data accuracy, and disclosure of financial COIs are all potential snares for journals and scientists.

Authorship of a published paper is extremely important to a scientist. The number of publications, the order of authorship, and the impact factor of journals all weigh heavily in the assessment of our academic productivity by us and our peers as well as by our research institutions and employers. While author order is an ever-present issue, it is one that is best addressed by the individuals involved in the scientific work. Of greater concern on a larger scale is the potential for “ghost authorship,” where authors take credit for work they did not perform themselves. This can occur in an academic setting in which an author takes credit for the work of another author such as a student, trainee, employee, or colleague. It can also occur in the setting of pharmaceutical or medical implant manufacturers if a scientist takes credit for the work of an employee or consultant of the company. It is, in effect, a nonmonetary reward to the physician given the aforementioned benefits of being a published author. Oftentimes, the authors are also paid by the company for the published work, compounding the ethical dilemma.

Legal documentation associated with scientific literature has typically been focused on copyright transfers of the text and images from the authors to the publisher. Given the pitfalls under discussion, an increasing amount of documentation is required to identify authorship, institutional review board approval, and financial relationships. The completion of these forms can be both onerous and time consuming. Not surprisingly, they are often treated superfluously, with individuals, at times, signing forms for coauthors. Despite appearing innocuous in practice, this act can be interpreted as forgery and can have significant legal ramifications.

The peer-review process at many journals is meant to ensure the accuracy and quality of printed publications. Articles are intensely scrutinized for an inadequate hypothesis, poor methodology, inappropriate statistical analysis, or faulty data interpretation; however, the current process is based entirely on the assumption of truth in the reporting of data. It is an assumption traditionally afforded to all authors. Fabricated data can be so well crafted that it is very difficult, if not impossible, to determine the validity of the presented data. While authors are often required to sign documentation attesting to the accuracy of their work, this measure, as discussed previously, probably does little to prevent abuse. When such instances come to light, the author has placed his or her reputation and career in jeopardy. The fact that such acts nonetheless continue to occur highlights the lack of concern that dishonest authors have of being discovered.

A thread that binds these pitfalls together is the potential for outside interests to trump the scientific process. While authorship and publications provide certain nonfinancial rewards, it is the specter of financial gain and corporate influence that garners the most attention and concern. Relationships between clinician-scientists and medical industries have been instrumental in creating innovations in health care, advances in technology, and improvements in the treatment of medical diseases. Financial relationships between both parties are essential to fund research and offset the cost of treatments that are otherwise deemed experimental and are therefore unpaid by private or public payers. Stagnant or shrinking public dollars for research has further cemented the corporate sector as a critical source of funding. Additionally, scientists (like all workers) and institutions are compensated for the work and effort required to conduct research.

These relationships also create the potential for bias. Across a number of scientific journals and medical specialties, it has been shown that most industry-funded publications report positive results favoring the investigational drug or device, with only a minority reporting no benefit or harm (negative results). Why is this so? It is often suggested as proof of a nefarious collusion between industry and scientists to promote lucrative treatment options. Certainly the environment is potentially ripe for overt bias, which can exist when financial or corporate entities own or control the data and results of a study. In such cases, negative or marginal results may not be published because of the potential negative financial impact. While studies conducted under such conditions are often rationalized as the internal trial and error of product research and development, the involvement of patients and nonemployee physicians or scientists fundamentally alters the nature of the investigation and opens it to outside scrutiny. Scientists themselves may also selectively publish positive results to maintain lucrative avenues of research funding and personal income or to pro-
Pitfalls in the publication of scientific literature

tect companies in which they have ownership, personal investments, or intellectual property.4

While such acts are clear and obvious sources of bias, they are very likely to be uncommon. More pervasive, and therefore more difficult to detect or control, is the potential for COIs to affect clinical research in unintentional ways. The financial consequences of producing positive findings can influence patient treatment, data collection and analysis, and manuscript preparation without the scientists’ or companies’ overt knowledge. Beyond a purely vested financial interest, the parties investigating new devices or drugs often have a strong personal or emotional belief in the treatment that may further bias their observations and limit objectivity. Additionally, knowing that positive findings are more likely to be published, research that produces only negative findings may be abandoned. Clearly, these overt and subtle conflicts can negatively affect both the quality of the research and the analysis of the data, leading to a skewed interpretation of the results. Unfortunately, not until investigational treatments reach the general market can postmarket surveillance and third-party research quantify the true impact of conflicts and bias.

The potential for financial COIs for peer reviewers, journal editors, and publishers is also an important issue requiring consideration. Peer reviewers, although often blinded to the identity of the authors, may nonetheless be able to deduce the involved authors or institutions based on the content or style of the manuscript. Reviewers can bring with them their own positive or negative biases toward the investigational device or drug. Even journal editors may be influenced to preferentially offer studies with positive rather than negative findings. Papers discussing the merits of new technologies have historically garnered high readership and a larger number of secondary references both in the lay press and the scientific literature. Readership, references, and lay press accolades all increase the prominence and influence of the journal. Last but not least, corporate advertising may account for a large share of the operating budget and profits for the publishers of medical journals. When reading many major medical and surgical journals, it can be difficult to find actual scientific content in a sea of advertising pages. Again, this financial relationship between industry and journal publishers creates the potential for COIs that may influence the acceptance or rejection of certain manuscripts.

Response to Critical Events

A number of critical events have occurred over the past few years that have brought the issues of COI to the attention of the scientific and lay communities. The response of scientists and journals to these events has varied and has demonstrated how unprepared these communities have been.

Editorial Responses

The response by scientific journals to these events has varied drastically with no clear, uniform process to address situations of potential conflict or academic dishonesty. Responses have ranged from no response to a formal retraction to active engagement in the dispute.

In instances of confirmed academic dishonesty, some journals have retracted the questionable article and provided a written explanation for their actions.10,13,17,21 In response to the work of Rueben and Ekman,17 the editor-in-chief of The Journal of Bone and Joint Surgery (American) retracted the paper and stated that the article as well as a review article by the same author was based on fabricated data created by the lead author.10 In response to the work of Kuklo et al.,13 the editor-in-chief of The Journal of Bone and Joint Surgery (British) retracted the article over claims of forgery and data fabrication.21 The editors additionally banned the lead author from further publication in their journal. While scientifically appealing, these responses have left the press and lay public wanting further retribution despite the lack of substantiated proof.

In contrast, other editorial responses have only contributed to the surrounding controversy. Robinson et al.18 reported on the efficacy of escitalopram in the prevention of poststroke depression in a prospective randomized study. Shortly after publication, independent researchers informed the publishing journal as well as the general public about an undisclosed COI between the lead author and the drug manufacturer. The editor’s reported responses included disparaging remarks about the researchers in question and communications with their dean about the allegations. Although the editor has denied any such tactics, the general public is left with the impression of a defensive editorial hierarchy wherein interests of self-image, reputation, and financial gain trump science and the public good.

Author Responses

There has been little formal response from the authors involved in these high-profile situations. Almost all have defended the integrity and accuracy of their work. None has believed that any COIs affected their role in the study, the study’s validity, or the interpretation of the results. In instances of insufficient or inaccurate disclosures, authors have explained these instances as either an unintentional oversight or an insignificant relationship. Appropriately so, the authors have often not publicly responded to issues addressed in the mass media as the legal implications of these allegations remain to be seen.

Professional Organizational Response

Professional organizations have made no formal response to these examples of inadequate disclosure. Although reforms are actively ongoing within these organizations, the relative silence has increased skepticism. In some instances, the involved authors may be prominent members of professional organizations. In other situations, the organization itself may have financial ties to the involved corporate entities.

Although relatively silent on specific occurrences, professional organizations have taken many proactive steps to address the conflicts that arise in scientific work. Nearly all orthopedic and neurosurgical organizations now require open disclosure of all financial COIs. This information is made available to all organizational members and at scientific meetings open to the public. Moreover, leadership and educational positions within or-
ganizations often require open disclosure of all potential financial conflicts.

**Governmental Response**

The high-profile nature of these situations combined with the cost implications and political advantages of addressing these problems creates an environment ripe for a state or federal response to the larger issues of financial conflicts in health care and research.

While the federal government has not yet passed any law specifically regulating medical research COIs, many examples of government regulation of COIs between physicians and industry do exist. Disclosure of all significant financial relationships (more than $10,000 or 5% equity in a company) from investigators seeking government funding (from the National Institutes of Health or the Centers for Disease Control and Prevention) has been required since 1995. The FDA has also required all investigators applying for drug or device approval to disclose significant financial interests (over $50,000) since 1998. More recently, in 2004, the US Department of Health and Human Services issued the document “Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection.” These guidelines recommended that investigators disclose industry relationships to potential research volunteers. While no significant penalties or regulations were associated with these guidelines, in Moore v. Regents of the University of California the court did find a physician investigator liable for not disclosing his COIs to a research volunteer. It is anticipated that ongoing legislative proposals and investigations will lead to laws specifically regulating the potential influence of industry on the production and publication of medical research.

Specific legislators have shown concern regarding potential COIs that have existed in medical publication. Senator Charles Grassley (R-IA) has written a letter to the editors of 8 well-known medical journals (American Journal of Medicine, Annuals of Internal Medicine, Annual Review of Medicine, Archives of Internal Medicine, Nature Medicine, PLoS Medicine, JAMA, and New England Journal of Medicine) expressing concern regarding ghostwriting. In a report dated June 24, 2010, (http://grassley.senate.gov/about/upload/Senator-Grassley-Report.pdf) Senator Grassley requested responses to 5 specific questions regarding each journal’s position and policies on ghostwriting, author disclosure of industry relationships, journal disclosure of any industry role in the development of a manuscript, and whether each journal had taken any action against an author failing to disclose involvement of a third party in manuscript development. According to a report by 2 New York Times writers who had obtained the editors’ replies, the responses varied considerably regarding journal policies and disclosure, except that no journal or editor had taken action against an author for failing to disclose third party ghostwriting. Senator Grassley has also recently asked 23 medical schools for information regarding their COI policies as well as their policies on the disclosure of financial relationships between medical school faculty and industry.

A new set of Massachusetts laws, entitled the Pharmaceutical and Medical Device Manufacturer Code of Conduct, has gone into effect. These new laws (http://www.mass.gov/Eehhs2/docs/dph/regs/105cmr970.pdf) restrict gift giving to physicians and also require public disclosure of all payments made to physicians starting July 1, 2009. The laws require annual disclosures of “the value, nature, purpose and particular recipient of any fee, payment, subsidy or other economic benefit with a value of at least $50” to any health care practitioner. The current laws may not have significant bearing on the research and publication activities of Massachusetts clinicians, however, given that the definition of “sales and marketing activities” included in the proposed regulations excludes payments made as reasonable compensation in connection with a genuine research project or clinical trial. It is anticipated that future amendments will include disclosures related to research. Other states, including Wisconsin, Oregon, Minnesota, Connecticut, Iowa, Maryland, and Vermont, have similar existing or pending legislation.

Senators Grassley and Herb Kohl (D-WI) introduced perhaps the most significant related legislative proposal in January 2009. The Physician Payments Sunshine Act of 2009 is intended to improve transparency regarding the relationships between physicians and industry. The act would require medical device and drug manufacturers to publically report any payments over $100 made to physicians, regardless of the reason for payment. Public reporting of payments in support of research or in support of publication would specifically be required. This act is supported by at least 1 industry organization, the Pharmaceutical Research and Manufacturers of America (PhRMA). The American Academy of Orthopedic Surgeons as well as other physician and physician investigator organizations are currently working with Congress on the Physician Payments Sunshine Act, which has garnered widespread support. Many expect it to become law in the near future.

**Solutions**

While changes to state and federal laws may be anticipated in the future, governmental regulation should not be the primary solution. Optimal strategies to address these pitfalls need to be initiated by physicians, scientists, and medical journals. The goals of any strategy should be to limit the extent of industry involvement in these studies and to make transparent any financial relationships that may contribute to a lack of objectivity and affect, either intentionally or unintentionally, the outcomes of research.

**Responsibilities of the Physician-Scientist**

Physicians facilitate the delivery of new technology to the market by conceiving innovative ideas, acting as members of scientific advisory boards, managing clinical trials, offering initial feedback on these products, and teaching these methods to other practitioners. Not surprisingly, it has been estimated that up to one-third of lead authors may retain some sort of financial interest in their research. Physicians are bound by the Hippocratic Oath to place the welfare of their patients first and foremost above all other concerns (beneficence) while pro-
Pitfalls in the publication of scientific literature

tecting them from undue harm (nonmaleficence). Since most clinicians freely accept this ethical obligation, some believe that their intellect, training, and principles serve to insulate them from external sources of bias and view any mandatory COI benchmarks as a personal affront. However, rather than contest the imposition of these restrictive regulations, it is imperative that physicians take the lead and accept that they are subject to a higher standard than others, including contemporaries in business, law, and politics. By confronting the challenges posed by industry COIs head-on and recognizing the need for accountability, physicians can take a proactive role in elaborating policies that are both effective and practical.

To this end, clinician-scientists need to take active steps to manage the potential COIs that may arise as a result of industry funding for their investigations. While avoiding industry funding of scientific investigations is one approach, it is important to recognize that the establishment of partnerships between physicians, scientists, and industry is often in the best interest of the public. When the avoidance of industry funding is not feasible, it is essential for physicians to abide by the concept of full disclosure of all relevant COIs as defined by the specific journal to confer absolute transparency to the readers. Physicians should also be cognizant of the myriad ways in which their scientific inquiries may be affected by COIs and take every precaution to ensure that the study design, statistical analysis, and manner in which the findings are presented are as free of outside influence as possible. Before agreeing to perform research projects in conjunction with corporate entities, it is critical that surgeons formalize the terms of these agreements and maintain explicit permission to independently and accurately report the results so that any unfavorable results are not mitigated or even suppressed altogether. It may be reasonable to assume that in the near future, authors who possess financial ownership in an industry-supported venture will be expected to recuse themselves from any aspect of the investigation. The widespread adoption of these and other strategies will curtail any industry infringement on scientific research and will allow physicians to focus on the interests of their patients above all others.

Responsibility of Journals

Although this discussion has cited a number of unfortunate examples of actual or perceived ethical violations related to scientific authorship, the majority of situations in which COIs are inappropriately or inadequately disclosed occur unintentionally. Regardless of intent, however, such occurrences cast a shadow on the medical community and threaten the integrity of journals.

There is ample evidence suggesting that the widespread prevalence of COIs among the authors of scientific articles is an ongoing problem. While formal COI regulations were first introduced by editors more than 20 years ago, a significant proportion of authors have been largely noncompliant with these measures in the past. Even within the past few years these policies have been exceedingly vague, with definitions of COI that are either too broad or too narrow in scope. In addition to the significant discrepancies among the disclosure requirements of different journals, it is also clear that up to this point these directives have not been strongly enforced by editorial staffs. Even when these safeguards are in place it is difficult to ascertain what they actually entail; according to one assessment, nearly 50% of all randomized clinical trials published in several major orthopedic subspecialty journals did not elucidate the measures initiated to reduce any bias in the studies.

Therefore, journals must also take steps to enhance the management of COIs. The optimal method for minimizing the influence of industry in research is to eliminate all such entanglements universally. But because the prohibition of outside support for scientific investigations is largely impractical, focus should shift to improving the means by which these affiliations are revealed to the public to create an environment of complete transparency. Journals need to furnish thorough and comprehensive guidelines for authors to mitigate ambiguity about which industry affiliations warrant acknowledgment. This should be independent of the authors’ individual assessment of potential conflict. Beyond reporting monetary values, published disclosures must characterize the nature of their involvement, for example, recipient of grant support or royalties, consultant, stockholder, member advisory board, and so forth. Without exception, all of these data should be listed for every author so that it is readily apparent to the readers. Confirmation of these disclosures may be accomplished through prepublication contact with the authors’ institution or employer. These regulations should not be viewed as voluntary, but as obligatory for all submissions including original research, reviews, editorial responses, and consensus statements. Every article may be subject to the prejudices of its authors, regardless of its format. Given the continuing disparities that exist among many disclosure policies, a standardized framework by which COIs can be reported for authors can improve consistency in the scientific literature. At this time, various editorial organizations such as the World Association of Medical Editors, the Committee on Publication Ethics, and the International Council of Medical Journals have all made recommendations in an attempt to promote greater uniformity among publications.

Conflicts of interest are not limited to the authors of scientific research but can also adversely affect the judgment of peer reviewers and even the editorial staff. In theory, anyone who has access to a manuscript could conceivably appropriate ideas from other investigators or even delay an article’s publication to further their own competing agendas. In a survey of 135 biomedical journals, only a minority asserted that they currently monitored the COIs of these other groups. For this reason, journals must also expand these same disclosures so that any involved reviewers or editors are held to the same expectations as the authors themselves.

Above all, journals must remain vigilant to make sure that these COI guidelines are closely adhered to in order to preserve the sanctity of the scientific literature and secure the trust of the readers. Nevertheless, should it be necessary, the editors must be prepared to act quickly to scrutinize any cases of suspected impropriety and willing to implement sanctions as needed. When successfully implemented, these strategies will protect the well-being...
of not only the patients and the public at large but also the scientific investigator. A greater degree of scrutiny will ultimately add credibility to those authors and studies selected for publication.

Conclusions

Increased scrutiny of physician-industry relationships has largely been perceived as a detriment to the provision of health care. The lay press in particular has promoted the perception that clinicians have been motivated primarily by greed rather than the welfare of their patients. On the contrary, these collaborations have given rise to significant advances in medicine. Although the mere presence of a COI is not necessarily a sign of wrongdoing, even the impression of impropriety is sufficient to cast doubt on a physician’s clinical judgment or research investigations. Solutions to improve the quality of medical literature should be based on improved transparency of COIs, mitigating bias associated with COIs, and a greater degree of scientific and professional scrutiny over the potential affects of COIs.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Patel, Fehlings, Vaccaro. Acquisition of data: Patel, Whang, White, Vaccaro. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors.

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Accepted August 17, 2010.

Please include this information when citing this paper: published online September 17, 2010; DOI: 10.3171/2010.8.JNS091834.

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A. A. Patel et al.

26

J Neurosurg / Volume 114 / January 2011