Good publishing practice

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This comment refers in part to ‘Relations between professional medical associations and the health-care industry, concerning scientific communication and continuing medical education: a Policy Statement from the European Society of Cardiology’, by ESC Board on page 666 and ‘Conflict of interest policies and disclosure requirements among European Society of Cardiology National Cardiovascular Journals’, by F. Alfonso et al., on page 587

Writing and information

The history of mankind really began with the advent of writing. As information grew in complexity, its representation in writing systems involving letters, numerals, and other markings became a necessity. The system of writing invented by the ancient Sumer in Mesopotamia some 5000 years ago enabled information to be preserved and accessible and, in turn, forms the cornerstone of our modern information society. Since then, the internet permits unrestricted access for everyone to virtually everything we know. The relevance, quality, and trustworthiness of an overwhelming amount of information have thus become a key issue, particularly in the scientific literature.

A changing environment

Two developments are noteworthy in this context: first, the ethos of academic institutions has changed with their increasingly close collaboration with business and industry. The search for truth within the ivory tower is no longer the primary mission of universities, scientists, and physicians; indeed, the commercialization of their knowledge and products has become an additional strategy. In 1980 the US Congress passed the Bayh–Dole Act which allowed universities to patent discoveries made possible with federal grants. Shortly thereafter, the US Supreme Court decided in the case Diamond vs. Chakrabarty that genetically engineered organisms are patentable. Given the declining number of federal grants, such novel opportunities were welcomed by most academic scientists and physicians, but they obviously introduced unprecedented interests into the scientific process. Despite this, European universities eagerly followed the example of their American colleagues.

Secondly, the introduction of randomized clinical trials by Sir Austin Bradford Hill (1897–1991) in 1948 not only has changed the treatment of tuberculosis, but even more so the requirements for clinical evidence and, as a consequence, those for the development of drugs and later also devices. Half a century ago, the US Food and Drug Administration (FDA) did not have authority to require drug manufacturers to demonstrate efficacy and reasonable benefit–risk relationships of novel drugs. In 1961, US Senator Estes Kefauver introduced legislation that—in response to the thalidomide scandal that had evolved in Europe and Australia—eventually gave the FDA authority to force pharmaceutical companies to provide efficacy and safety data before the introduction of their products into the market. Over the years, such legislation was adopted by most European registration agencies, including the European Medical Evaluation Agency (EMEA). This made double-blind, controlled, and randomized clinical trials mandatory for drug development and changed the practice of medicine, particularly in the cardiovascular area. Obviously, such trials could not be performed without a close collaboration of academic scientists and physicians with industry. Although this led to an enormous boost in the quality and amount of clinical research, it again introduced novel interests in academia that increasingly attracted the attention of investigative journalists, politicians, and the public at large. Thus, the quality and trustworthiness of the publication process and its products has come into question recently—and this requires a credible response.

Publishing is communicating

Publishing makes scientific writing available—only findings that are published exist. From the ancient Greeks to modern science, discoveries have been written down in books and papers for the use of current and future readers. Over the centuries and particularly over the last decades, the number of scientific journals and publications has increased tremendously; indeed, in 2010 more than 38 000 scientific papers were published in close to 40 000 journals worldwide, and it is anticipated that with the rise of China and India as scientific nations, this number will increase...
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best scientific information. Who is a peer? A peer is a person of

of the same civil rank or standing, an equal before the law as The

American College Dictionary" puts it. In science and medicine, this

would be a colleague of similar experience and knowledge, in short: an expert in the field. It is said that Henry Oldenburg

(1618–1677) the long-time secretary of the Royal Society, introduced the system when he was editor of the Philosophical Transactions. As a theologian he did not feel competent enough to judge all the papers submitted and thus relied on the judgement of colleagues from other fields. Ever since the system has been adopted by most journals in science as well as in medicine.

Currently, most journals use two to five reviewers for submitted papers. Editors, with the help of such experts, base their decisions on distinct criteria such as originality, importance, appropriateness of the methods and statistics used, as well as the quality of illustrations and the discussion. Commonly, the reviewers remain anonymous to the submitting authors. Although the appropriateness of the anonymity of the peer reviewers has been debated, it certainly does ensure a more open assessment and rating of manuscripts and it avoids future personal conflicts between authors and reviewers.

Less than perfect

While the peer review system is widely used, it has remained controversial. Indeed, what can be said about the peer review system has been said by Churchill about our political system: ‘Democracy is the worst form of government, except for all those other forms that have been tried from time to time.’ Every editor receives letters from authors who are disgruntled about the quality of the reviewers assigned to their rejected manuscript. Further, peers—and for that matter editors—may not always be as qualified as they should be, they may not always be as thorough as they are supposed to be, and they are not necessarily free of

conflicts of interest of a personal, scientific, or financial nature. While we are beyond the times when the Inquisition of the Catholic and other Churches mistreated or burned eminent scientists such as Galileo Galilei, Giordano Bruno, or Michel Servet, even recent history is full of examples where prejudices, rivalry, and jealousy have delayed or hindered scientific discoveries, for instance the one made by Werner Forssmann. Furthermore, strong believers in certain concepts, in paradigms, as Thomas S. Kuhn would put it, can still make it difficult to accept novel findings. It appears, however, that in times of ‘normal science’, the peer review system works reasonably well, particularly if several experts are invited to assess the value of the work submitted. Importantly, if personal or financial conflicts exist, reviewers should decline an invitation to review. Many journals, among them the European Heart Journal and its affiliated journals, have therefore included such a statement in their invitation letter to potential reviewers.

The second problem, however, remains: what is the quality of the information we get? Is the question raised relevant? Are the methods used appropriate? Is the statistical analysis correct? Have the data presented really been obtained? And lastly, are the results relevant for clinical application?

The peer review system

The peer review system

The position of the European Society of Cardiology

The White Paper of the European Society of Cardiology (ESC) published in this issue discusses these issues carefully with a particular focus on conflicts of interest. The document states that ‘All manuscripts must be subject to anonymous, independent peer review. There should be independent statistical review of every accepted manuscript. Members of the editorial board and reviewers should decline any invitation to edit or review any manuscripts relating to topics, drugs, or devices in which they have significant commercial or academic interests.’ Thus, scientific journals are expected to implement a strict policy to meet such requirements. Only under such circumstances can published work fulfill the criteria of ‘certified knowledge’.

In another paper also published in this issue of the European Heart Journal, the editors of the national journals of the ESC report on a survey analysing such policies in cardiology journals in Europe. They found that most journals do indeed have such a policy, particularly disclosure of financial conflicts, but only 57% published that of all authors. Although most journals inform potential reviewers in their invitation letter to decline the request in the case of conflicts, it remains difficult for the editors involved to exclude potential bias of their reviewers—they must rely on their experience and on trust.

What is a conflict?

After all, what really is a conflict? The word ‘conflict’, derived from the Latin word conflagere, means to come into collision, to clash. In a conflict as discussed here, two sorts of interests collide: scientific integrity and the desire for personal or financial success. Such desires may be conscious or not, but may lead to biases. The term ‘bias’ means tending or leaning towards a particular outcome. Obviously, numerous biases can arise in the scientific process and in publishing. First and foremost, authors may want to prove pre-conceived notions and to advance their careers. Indeed, although Sir Karl Popper saw the scientific process evolving
between conjectures and refutations, scientists truly strive to prove rather than falsify their own notions and hypotheses. This behaviour reflects the basic motivation of researchers as well as the incentives of the academic reward system. This will not pose a problem as long as editors and their peers ensure that the enthusiasm of authors for their findings is supported by appropriately obtained and analysed data and that the results and conclusions are discussed in a balanced manner. Although to the best of our knowledge no statistics exist on the degree of concordance or discordance of reviewers, it appears that in most instances they agree to a large extent on the quality of a submitted manuscript.

Recently, new conflicts have arisen: in some instances, authors may want to gain direct or indirect financial benefit from their research. An increasing number of findings leads to patents, and obviously such results are intended to translate into marketable products. Under such circumstances, it cannot be excluded that the question raised and the patient set chosen are intended to optimize the results, that unfavourable data are not presented, and that the interpretation and conclusions are overly optimistic. Since financial ties are not visible, full disclosure of such relationships must be required, as again outlined by the ESC White Paper. Although the availability of such information by itself does not solve the problem, it will help the editors and reviewers to ask the right questions and request appropriate revisions of the manuscript. Furthermore, it helps the reader to assess critically potential biases in the published paper —possibly with the help of a balanced editorial.

Obviously, publishers and editors are also prone to conflicts. First and foremost, publishers want to sell their product and editors want their journal to be successful. Large trials that involve a substantial purchase of reprints by the sponsor are as equally attractive as juicy findings that are taken up by the lay press and media and make the journal visible. Certainly, a 1998 article linking measles, mumps, and rubella vaccine to autism was accepted, although the number of patients was admittedly small and the potential implications huge. The paper received enormous press coverage—and was later found to be based on fraud (see below). Editors must be aware of such potential biases in their decision process and should not allow themselves to be seduced by media attention and potential sources of income. To that end, they must stand firm against pressures from industry, if required.

**Reverse conflicts**

Lastly, the most stringent critics of conflicts may themselves have a conflict. Indeed, the attention that critics of industry-sponsored studies receive in the media may introduce a bias as well, since they are usually heavily cited in articles, interviews, and TV features. In addition, not all of such criticisms have stood the test of time. In 1995 *Circulation* published a meta-analysis in which the authors claimed to demonstrate a dose-dependent increase in myocardial infarction with calcium antagonists which apparently had been denied by industry. The methodology was criticized, particularly the part related to dose—response, which is why the journal invited three editorialists to comment. Later, others also suggested biases in studies on calcium antagonists, if sponsored by industry. In the large ALLHAT trial, sponsored by the unsuspicious NIH, however, Curt Furberg and colleagues could not confirm their initial findings since amlodipine fared very well even when compared with an angiotensin-converting enzyme (ACE) inhibitor, as other calcium antagonists did in subsequent controlled trials. Thus, we do not get closer to the truth by simply uncovering conflicts—in the end it is the reproducibility of scientific findings—the unbiased search for truth—which is essential and not the discussion on conflicts alone.

**The worst**

It should be stressed, however, that conflicts are distinct from fraud; indeed, although authors with conflicts of interest report the data as they are, the conclusions they reach may not be fully supported by the data and the implications they foresee may be overstretched. On the other hand, fraud involves partial omission or fabrication of data. Unfortunately, while the ethos of science assumes a disinterested and honest pursuit of truth, not all members of the community comply with such a requirement. Indeed, just recently the UK’s General Medical Council found Andrew Wakefield from University College London guilty of dishonesty and serious scientific misconduct. It was found that his now retracted paper published in the *Lancer* in 1998 linking measles, mumps, and rubella vaccine with autism and bowel disease was ‘elaborate fraud’. Similarly, the Dutch psychologist Diedenk Stapel falsified data of numerous studies. He managed to conceal the fraud for so long because of his elaborate methods, whereby he fabricated data sets that he supposedly had obtained from collaborating scientists, thereby concealing the fraud from his post-docs. In November 2011, Erasmus Medical Center in Rotterdam fired Don Poldermans, a well-known cardiovascular clinical researcher, for violations of academic integrity. In a statement, the Erasmus Medical Center said that Poldermans was careless in obtaining his results and used fictitious data to prop up his findings.

What can editors and their peers do about this? Obviously, they cannot prevent fraud from being published; indeed, particularly the most sophisticated fraud is hard to uncover, as outlined above. Nevertheless, editors should be cautious in accepting small sets of data, just because of their appeal, the current fashion of science, and potential for press coverage. Furthermore, reviewers should be aware of such behaviour, particularly when data appear too good to be true.

**Editors’ expectations**

What do editors expect from authors? First of all, papers must be submitted according to the instructions for authors. It is unfortunate that journals do not appear to be able to agree on a common format, but, with close to 40 000 journals worldwide, this is understandable. Most journals reject up to half of the submissions without review. Thus, to pass the first hurdle, the message must be crisp and clear and this is best achieved in the abstract, i.e. that part of the paper that is read first. In another paper soon to be published in a forthcoming issue of the *European Heart Journal*, Winnik and colleagues have analysed abstracts submitted to the ESC Annual Congress. Of note, abstracts on basic science,
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Table 1 Good scientific publishing: summary of requirements

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<th>Ethos of science</th>
<th>Structure of paper</th>
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<tr>
<td>Transparency</td>
<td>Authors</td>
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<td>Honesty</td>
<td>Only list those who have significantly contributed and gave their written approval before submission. Indicate individual contributions of each author in the submission letter</td>
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<td>Trustworthiness</td>
<td>Abstracts</td>
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<tr>
<td>Registration</td>
<td>Summarize the most important findings and the conclusions thereof</td>
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<td>Structure of paper</td>
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<td>Authors</td>
<td>Methods</td>
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<td>Only list those who have significantly contributed and gave their written approval before submission. Indicate individual contributions of each author in the submission letter</td>
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<td>Describe precisely how you have obtained data and/or recruited patients, what measurement techniques and what statistics you have used</td>
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<td>Results</td>
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<td>Only report results that you have obtained (in relative and absolute values) and that have not been previously published. Use state-of-the-art statistics to analyse your results and use figures with appropriate scales</td>
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<td>Discussion</td>
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<td>Conflict of interest statement</td>
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<td>Report any financial conflicts related to this manuscript of all authors individually</td>
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<td>Give credit to those who previously worked in the area by appropriate referencing</td>
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being late in publishing is the work of Rosalind Franklin who
already in 1951 made seminal experiments on the structure of
DNA. She showed her unpublished crystallographic pictures on
the helical structure of DNA to James Watson when he visited
her lab on 30 January 1953 and gave him an essential hint for
the groundbreaking publication in Nature on the molecular struc-
ture of nucleic acids together with Francis Crick. At the end of
their paper they acknowledged: ‘We also have been stimulated
by the unpublished experimental results and ideas of…

Dr. R. E. Franklin…’. In 1962, however, when they received the
Nobel Prize together with Maurice Wilkins, the name of the
dark lady of DNA was missing.

This leads to the question: who is an author? An author should
have made substantial intellectual contributions, specifically to the
conception and design, data acquisition or analysis and interpre-
tation, and drafting and/or writing of the study. Of note, authors
should also be able to take responsibility for part of or the
entire study and its content. It is obvious that particularly in clinical
research there is an abuse of authorship, and the International
Committee of Medical Journal Editors (ICMJE) therefore recom-
pended that the contributions of each author be outlined in the
submission letter. Further, authors should confirm that their
work has not been published elsewhere whole or in part, in
order to avoid double publications, which is clearly scientific
misconduct.

For the integrity of clinical trials it is of utmost importance that
the initial hypothesis and design as well as the anticipated statistical
analysis are defined from the very beginning. To ensure this, the
ICMJE recommended that trials should be registered and a
design paper be published before the results are analysed.

Conclusions

Thus, good scientific publishing is more demanding than it used to
be. Since ancient times, however, the basic principles of science, i.e.
precision and honesty, remain the most important. Additional
requirements must now be considered before submitting a manu-
script (Table 1). The peer-review process can ensure optimal
quality of published manuscripts, provided editors and their
peers perform a rapid and fair assessment of the submitted
work. While not perfect, this has clearly improved the level of re-
search considerably. We could certainly try to do even better, but,
while doing so, we should not forget Salvador Dali’s words: ‘Don’t
go for perfection, you will never reach it!’—and he certainly knew
what he was talking about.

References

1. Krimsky S. Science in the Private Interest. Lanham, MD: Bowman & Littlefield Publish-
Committee on Publication Ethics (COPE) GUIDELINES ON GOOD PUBLICATION PRACTICE. Why the guidelines were developed.
COPE was founded in 1997 to address breaches of research and publication ethics. Redundant publication occurs when two or more papers, without full cross reference, share the same hypothesis, data, discussion points, or conclusions. Action. (1) Published studies do not need to be repeated unless further confirmation is required.