

Freedom of Science – Can Industry Influence What Scientists Publish?

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The right of scientists to publish data from their preclinical and clinical studies is a much-cherished principle and is vital to the freedom of science. Indeed, full and candid reporting of results is essential for scientific advancement; without such disclosure research work would have much diminished purpose and no impact outside the centre or organisation where the work was conducted.^{1,2} Prevention of publication preserves ignorance and may cause other researchers to needlessly repeat work. This is also unethical as it requires that human beings are exposed to a certain risk associated with such studies again without need.

Data are considered to merit publication when they are regarded by journal editors as novel, valid, derived using correct study designs and methods and are correctly interpreted. They are then subject to a wholly independent, unbiased and anonymous peer-review process.³⁻⁵ This strict but essentially fair system, however, has recently been threatened when published papers that show results from studies that involve commercial products were perceived by the manufacturer to potentially harm their market position by the negative or unflattering results presented. In such instances, commercial organisations have attempted to block publication or force retraction of articles by taking legal action against the authors and their institutions. The purpose of this article will be to consider the right to publish in science, review cases in which commercial bodies have attempted to block this right and assess the damaging effects on scientific freedom when such action is taken.

Conduct and Communication of Medical Research

Some 20 to 30 years ago, clinical studies were performed most often by academic centres, especially studies in early stages of clinical development or more clinical-experimental studies. Nowadays, such studies are often conducted by contract research organisations (CROs) on behalf of commercial sponsors, e.g. pharmaceutical, medical device or biotechnology companies. The main reason for this shift is the much higher complexity of study performance mainly in terms of formal aspects, data quality, study performance, etc. It is unquestionable that a successful collaboration of commercial sponsors and CROs (i.e.

clinicians and scientists in these institutions and those collaborating outside these institutions) is essential for the development and improvement of medicines and medical devices. Publishing the results of such studies in respected scientific journals should be an integral part of this process. It is also unquestionable that all collaborators (e.g. clinical investigators, study sponsors, scientists, authors) included in industry-sponsored research should ensure that the study as well as its publication is performed in a responsible and ethical manner.

Conflicts Related to Communication of Industry-sponsored Research

In recent years, the development and publication of research relating to sponsors' products has often been criticised.⁶ Most of these concerns are addressed in good publication guidelines that apply to publications arising from industry-sponsored clinical studies of marketed products with the aim to reduce publication bias.^{7,8}

Non-publication of Findings that Do Not Support the Sponsor's Marketing Aims

Pharmaceutical companies have recently been attracting increasing public criticism and hostility over their failure to publish large quantities of their own data from clinical trials and have been accused of suppressing data unfavourable to their products.⁹⁻¹³ In any research work involving commercial diagnostic or pharmaceutical products or comparisons of products, the publication of negative data is bound to be disliked and possibly opposed by its respective manufacturers and marketers. Any company is bound to have invested significant capital into the development of a product and has a position to defend. These market and financial pressures can cause some companies to put profits ahead of ethics and move them to obstruct the publication of legitimate data. While understandable, such action is indefensible as the welfare of patients is clearly the higher good than the profits of a given company from an ethical point of view.

In fact, when industry-sponsored research is performed in collaboration, e.g. with a CRO or medical writers, companies in general should grant all authors full access to data and support their freedom to publish the study results according to clear scientific criteria.

Interpretation of Published Industry-sponsored Research

It is important for authors to ensure that scientific results are presented in a responsible and balanced manner, particularly during the development of industry-sponsored publications with a financial interest, e.g. those describing products that the company markets. In addition, conclusions must be supported by the data and attention should be drawn to any limitations of the study. Such concerns should also be taken into account during the peer-review process (see below 'The Publication Process') when scientific research is submitted for publication in a medical journal.

In this context, everyone should be aware that the interpretation of published scientific research, e.g. by manufacturers for commercial purposes, should be treated with caution (they have to meet legal requirements of fair competition) and must be clearly distinguished from the actual content of a publication.

The Publication Process

Publication of the results of biomedical research in a scientific journal is a common practice to communicate scientific work and is not unique to industry-sponsored research. Today, most medical journals follow a peer-review process for the assessment of scientific work submitted for publication. The process of publishing scientific work using peer review was first established nearly 350 years ago when 'The Philosophical Transactions of the Royal Society' in the UK was established.^{14,15} Since that time, particularly during the 20th century, there has been an explosion in scientific endeavour and a phenomenal increase in the numbers of journals to report the consequent avalanche of specialist scientific information.

Over time, the freedom of scientists to publish has been regarded by many as a 'human right'^{16,17} and the process involved has become more established and follows a similar pattern in most journals:

- After submission the editor has a first look at the manuscript (MS) and decides whether it is suitable for the journal and worth sending out for anonymous peer review or rejects it and returns it to the authors.
- Peer reviewers who should be experts in the area of research the MS is dealing with are selected by the editor. They should provide a detailed and constructive written commentary on the MS. The reviewers should also make recommendations about potential publication of the MS as submitted or ask for specified amends or advise rejection of the MS in a separate document to the editor.
- The editor has to read the comments of the reviewers (most often two, sometimes three) and decide if he/she believes the MS is worth revision or not.
- In the latter case, the MS is sent back to the authors with the reviewers' comments and the information why it is rejected.
- In the case that the MS may be worthy of publication in the given journal, the editor will send the MS back to the authors along with the reviewer's comments and ask them to revise the MS according to these comments.
- The authors are required to revise the MS and will send in a revised version with all changes clearly marked and a response letter describing in detail how the comments were handled.
- The editor will read the revised MS along with the response letter and make a decision about acceptance.
- If accepted the MS is forwarded to the publisher to start the publication process itself.

Criticism of Published Research in a Scientific Manner

The peer-review system has its shortcomings and is not without its critics,^{3,14,18} but being answerable only to responsible editors and fellow scientists it is fundamentally democratic. If readers or groups with vested interests object to any published data, the methodology used to obtain it or its interpretation, they have the right of reply and can submit an objection or commentary to the journal. If the objection is apparently valid, a decision that is usually made by the editor, the journal will:

- Publish the objection or criticism as a letter to the editor addressing a specific publication.
- Allow the authors of the original paper to respond in print.
- If necessary, publish an amendment or erratum to the original paper.
- In extreme cases, retract the original paper and declare why. Such cases have happened in recent years when it became clear that the authors had committed scientific fraud or had plagiarised others' work.

A Recent Attempt to Force the Withdrawal of a Publication

It is widely known and often discussed that companies fail to publish all their own data from clinical trials and suppress data unfavourable to their products.⁹⁻¹³ However, attempts to block publication of industry-sponsored research performed by external partners (e.g. CROs) are less common or at least this was not reported that often until now.

A notable and disturbing challenge to the existing freedom of publication arose recently after a group of researchers from a diabetes technology research institute in Germany published a comparative investigation of the accuracy of various commercially available blood glucose monitoring systems that were produced by a range of manufacturers. The results were published in a US-based scientific diabetes technology e-journal after a complete peer-review process.¹⁹ The accuracy of blood glucose monitoring systems in diabetes therapy is critical as incorrect readings could lead to inappropriate insulin dosing resulting in either acute metabolic deteriorations (with diabetic coma and even death due to severe hypoglycaemia) and/or non-optimal long-term metabolic control. The work presented in the publication mentioned above was supported by a given manufacturer of blood glucose monitoring systems, which was declared in the scientific publication. The publication was subsequently used by the supporting company and at least two other companies for product promotion. The author and institution of the publication were challenged judicially by a European manufacturer and its resellers in various European countries (issued 'cease and desist' letters) because they did not agree with the results regarding their products tested in the study. The legal action demanded that the published article be withdrawn and the results not to be cited. The editors of the journal in which the results were published wrote a spirited defence of the original article in an editorial stating that attempting to force the withdrawal of these results would be an "unbelievable (and stupid) move" and a challenge to the freedom of science.²⁰

Internet Provides Worldwide Easy Access to Published Data

It is worth mentioning that the US journal involved in the above case publishes its data only via the Internet, i.e. in an electronic format (e.g. PDFs). Access to these publications is limited to the subscribers of this journal for a certain period of time, except when the articles were accessible via Open Access. The Internet allows users to gain

easy access to scientific publications from anywhere in the world. As a consequence, could companies initiate legal action against scientists in every country in which Internet is available?

Consequences of Legal Actions

While the legal actions against the author and his institution in the example mentioned above are likely to fail, the plaintiff has already punished the defendants even before the case reaches the courts. The reason being the cost of mounting a legal defence is significant. All the time required for an adequate handling of such legal actions imposes significant indirect costs that are difficult to quantify; furthermore, the costs of such legal actions can provide a serious threat from an economic point of view for small scientific institutions.

Despite a successful court outcome, according to local laws in many territories these costs cannot be recovered. Several such actions therefore could financially ruin the scientist and/or his institution forcing him to comply with the company's instructions to accept defeat and retract the data. This would not only be an injustice but would hide important data, seriously restrict the freedom of science and could potentially put patients with diabetes (in this example) at severe risk.

When manufacturers use inappropriate or disputed content of a scientific publication for commercial purposes including use in advertising materials, other manufacturers often take legal action against them. Such action, however, is definitely not an appropriate way to act against a scientific publication; submitting a scientific defence, a letter to the journal and/or publishing new data to support their case would be a far more suitable response.

Other Examples

The featured example concerned a diagnostic system for which lawsuits are rare, at least when it comes to addressing publications. In the pharmaceutical industry, however, there are legal precedents in which companies have sought to block publication by individuals and organisations of unflattering data regarding either efficacy or safety. Notable examples are:

- A clinical group in Denmark published a study showing increased kidney failure and haemorrhages among critically ill patients with sepsis receiving hydroxyethyl starch versus standard treatment. The German manufacturer demanded that the article must be withdrawn and amended due alleged 'misleading information' or they would take 'all appropriate legal steps' for compensation.^{21,22}
- A haematologist at a hospital in Toronto, Ontario, Canada, considered that the drug deferiprone, for which she was conducting clinical trials, was harming patients. Both the drug company concerned and the institution took action against the doctor and charged her and her colleagues with malpractice.^{23,24}
- A study in the US showed the bioequivalence of four synthetic thyroid drugs. The pharmaceutical company that sponsored the study (and marketed one of the drugs) took action to undermine publication of the results that included writing to the journal (*JAMA*) stating that the study was flawed.²⁵⁻²⁷ Publication was delayed three years but the author was vindicated. The company was eventually accused by the Federal Court of San Francisco of 'suppressing a medical study in an effort to control the American market for thyroid drugs'.
- A commercially sponsored retrospective study compared mortality in preterm infants with respiratory distress given one of four

surfactant factors.²⁸ One product was found to have a 49.6 % greater likelihood of death ($p=0.043$) versus the sponsor's product. The study authors and the sponsor were then sued by the other manufacturer for publishing a 'malicious falsehood' (libel). They also challenged the methodology, failure to cite a contradictory report, omission of data that would have produced a less-skewed conclusion and alleged conflicts of interest. A federal court in Buffalo, Indiana, US, however, concluded that 'peer-reviewed journals, not courtrooms, are the proper place to vet scientific disputes' and dismissed the charge of libel.²⁹

- The company marketing adalimumab for rheumatoid arthritis and other indications recently sought a legal injunction to block the European Medicines Agency (EMA) from releasing detailed information from clinical trials on the drug. The company claimed that it supported transparency of clinical research and safety information for the benefit of patients and healthcare professionals [but not] the disclosure of commercially confidential information that does not meaningfully contribute to the scientific review or evaluation of our products'.³⁰

Freedom of Access to Data

Many scientists believe that public disclosure of data of clinical trials is mandatory regardless of the results involved. An extreme recent case involved the publication of two studies in which the H5N1 avian influenza virus was modified making it transmissible between mammals. These papers could be considered as blueprints for a weapon of mass destruction but following extensive public debate, it was agreed that the studies should be published anyway.³¹⁻³³ The consensus appeared to be that responsibility rests with how scientific knowledge is used rather than who disseminates it. In the light of this, commercial sensitivity seems a poor excuse for blocking scientific publication; to intimidate or legally punish investigators who want to do this appears to be reprehensible. In addition, the International Federation of Pharmaceutical Manufacturers and Associations in its joint position statement specifies that all clinical trial information must be published or posted in a public database.³⁴

It is likely that the manufacturers of diagnostic kits, drugs and other medical products will be increasingly required to conform to these guidelines if they wish to remain in business. Further initiatives and codes of practice, however, may need to be established and enforced to prevent future cases in which commercial bodies seek to gag scientists who would publish inconvenient truths.

Conclusion

Industry-sponsored research and its publication should be performed in a responsible and ethical manner. The freedom of scientists to publish valid data is essential, including results pertaining to commercial products. They should not be forced to constantly look over their shoulders fearing legal retribution or harm to their careers from companies who market these products. Attempting to block published research is inappropriate and unscientific. It is simply not acceptable that:

- Important scientific data regarding the efficacy and safety of a product are withheld.
- Individual scientists/doctors are intimidated and suffer harm to their careers when they seek to publish data.
- Imposing expensive lawsuits may prevent academic and independent scientists from publishing their data.

Commercial operations should, however, criticise published research in a scientific manner when they feel their product has been unfairly or incorrectly represented. If the results of a study are used in promotional

material in any misleading way the competitors can start legal actions against each other, but should not address the scientists that have performed the study. ■

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