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COMMERCIAL INFLUENCE IN HEALTH: FROM TRANSPARENCY TO INDEPENDENCE

Achieving greater independence from commercial influence in research

As part of The BMJ's campaign for greater independence from commercial influence in the creation and use of evidence, **Joel Lexchin and colleagues** outline some approaches to minimise bias in clinical trials

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Since the end of the second world war, research in medicines and devices has roughly been divided between publicly funded basic and translational research and commercially funded clinical trials. While this division is far from absolute, most clinical trials are funded by drug and device manufacturers wishing to bring products to market.¹

Given that the results of these trials determine whether and how drugs and devices are reimbursed and used, the financial stakes are high, and there is

strong commercial pressure to ensure that the results are favourable. It is therefore no wonder that industry control of clinical trials leads to systematic biases that overstate the benefits and understate the harms of treatments.² Table 1 presents some examples of these biases and their effect on funding and the research agenda; how clinical trials are planned, conducted, interpreted, written up, and disseminated; which academic researchers conduct the trials in which institutions; and the way that regulatory agencies function.

Table 1 | Sources of bias in clinical research

Problem	Consequences
Funding and the research agenda	
Focus on drugs for markets with the greatest commercial return ^{3,4}	Few products are developed for diseases mostly prevalent in low and middle income countries
Planning, funding, conduct, and interpretation of trials	
Industry sponsored trials can have inferior comparators, active comparators in inferior doses, or less clinically relevant endpoints ²	Trials are more likely to yield statistically significant results that favour the sponsor's product
Members of ethics committees can have conflict of interest with sponsors ⁵	Acceptance of inferior trial design which puts patients at risk or increases the likelihood that the trial will not yield meaningful results
Principal investigators, including academics, have financial relationships with companies sponsoring trials ^{6,8}	Trials are more likely to be implemented and analysed in ways that favour outcomes desired by the sponsor
Negative results can lead to drugs not being approved or to lower sales ⁹	Negative aspects are under-emphasised in public communications about the trial by the sponsor
Sponsors of trials employ ghost writers to create manuscripts describing the outcome of the trial ^{10,12}	Trial results are interpreted in a way that is favourable to the sponsor in journal publications
Dissemination and publication of trials	
Editors have financial relationships with companies; journals earn revenue from advertisements and selling study reprints ^{13,15}	Can influence what is published
Trials with negative results are not published or published with a positive spin ^{16,17}	Literature is distorted, influencing medical practice and systematic reviews
Academic-industry relationships	
46% of faculty in the US in non-clinical departments (eg, basic science laboratories) have a relationship with industry ¹	Commercial priorities can shape research agendas in academic settings
Publication agreements between investigators and industry constrain authors' independence ^{8,18,19}	Distorts scientific literature by increasing the likelihood that publications feature language or scientific interpretations favouring sponsor; limits progress of science by restricting academic freedom
Academic institutions have financial links with or financial interests in a public or private company	Can interfere with the core missions of academic medical centres to advance medical science
Changes in institutional regulatory culture as a result of reforms favouring commercial interests	More permissive interpretation of safety signals and increased reliance on expedited development and approval pathways that permit trials with greater uncertainty to support regulatory approval

Financial conflicts of interest jeopardise not only the integrity of science, but the objectivity of education, the quality of care, and public trust in medicine.^{20,21}

Since the pharmaceutical industry will continue to have a central role in researching new drugs and bringing them to market for the foreseeable future,

we consider how the most serious negative effects of commercial influence on clinical research can be reduced.

Reducing bias in clinical research

Our proposals for reducing bias—which come from our individual and collective research on the topic and our involvement and discussions with other experts, non-governmental organisations, and regulators—range from ones that are currently feasible to those impossible to imagine in the current political and economic climate. Although we present our proposals for different aspects of the research enterprise separately, we view them as part of an overall vision for the future directions of clinical research.

Public prioritisation of research agenda and funding

Clinical research efforts should favour innovations with the greatest potential to improve patient care and public health. One way to achieve this would be through a public process of prioritising areas of greatest medical need associated with a high level of public funding.²² Such a process would be able to prioritise drugs and devices for development based on their potential clinical value, focusing on diseases that are neglected, commercially unprofitable, lacking in effective treatments, or of particular importance for public health.

Reform the patent system and develop alternatives for product development

One major reform would be to change the patent system so that revenue is no longer the sole incentive for developing new drugs and devices and instead encourage more research on drugs that offer meaningful improvements in efficacy or safety and less on those that do not. If minor variations or combinations of existing products²³ that don't deliver greater therapeutic value were not patentable, there would be fewer clinical trials that waste precious resources developing products that are irrelevant to public benefit. India already forbids the patenting of a new form of a substance that does not enhance efficacy.²⁴ Other countries should consider similarly modifying their patent laws.

In place of patents, new national or supranational publicly funded research institutes would focus on the development of non-patentable products up to the point of readiness for clinical trials. This “public track” would fund the development of novel pharmaceutical molecules,²² which would remain in the public domain.^{25 26}

One model for these new forms of research institute is the Mario Negri Institute in Italy, founded on the principles of open science. It maintains its independence from commercial and state influence by ensuring that no funding from any source exceeds 10% of its income.²⁷ Its results are never protected by patents and are available unconditionally to everyone.

Product development partnerships, such as the Drugs for Neglected Diseases initiative (DNDi) are another existing alternative to relying on private industry alone to determine the research agenda. The partnerships do not conduct drug development themselves but integrate and coordinate multiple industry and academic partners and contractors along the drug development pipeline; allocate philanthropic and public funds to the “right” kinds of research projects; and manage research portfolios.²⁸ DNDi reported developing six new treatments for neglected diseases in its first decade of existence for the relatively low cost of around \$250m (£180m; €210m).²⁹ However, government contributions amounted to only \$2.6bn (out of a total of \$4.06bn) in 2018, far short of what is needed to deal with the many areas neglected by commercial

research. Governments need to make a much larger commitment to product development partnerships.³⁰

The private sector can also be encouraged to change research priorities through prizes, as a complement or alternative to the patent system.³¹

Restrict financial ties between researchers and funders

Rather than researchers being reliant on and in direct contact with commercial funders, money could be held and managed by public organisations. For example, the US National Institutes of Health or its equivalent in other countries could be authorised to oversee the design and management of clinical trials and the analysis and publication of the data that come out of them, allowing the separation of researchers from commercial influences.³² In particular, removing industry influence from pivotal trials—the ones that regulators use to make decisions about approval—is critical. In this case, trials would be planned, managed, and analysed by independent experts and would be funded from a central pool of money originating from companies. This proposal would be more feasible if major journals refused to publish trials with direct industry involvement. *The BMJ* has already adopted this stance with respect to tobacco industry funding, and other journals should be encouraged to follow suit.³³

Reducing industry control over the design of research studies might also result in less research waste. By one estimate, clinical trials could be conducted for a 10th to a 20th of the cost of industry driven research.³⁴ One reason why trials are so expensive is that it is necessary to enrol large numbers of people to generate statistically significant findings between drugs with marginal differences. The ability to reorient clinical research to focus on important clinical questions rather than the marketing needs of the sponsoring companies could decrease research costs.³⁵

Rethinking authorship and funding disclosures in journal publications

The International Committee of Medical Journal Editors guidelines defines authorship as “substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content; and final approval of the version to be published; and agreement to be accountable for all aspects of the work.”³⁶ However, this standard has not been consistently met and the definition can be manipulated to hide the sponsor's involvement in the design and publication of a manuscript.³⁷

Matheson advocates discarding the current definition of authorship and instead emphasising the process by which an article is created—for example, by naming companies as authors and identifying the drugs that the publication supports to allow readers to understand the commercial and scientific provenance of the article.³⁷ He also recommends that, if a company retains control or ownership of a trial database, it should be required to be listed as one of the first three authors.³⁷ An alternative proposal is to abandon the concept of authorship in favour of “contributorship,” which involves listing what each contributor did so that they can accept both credit and responsibility.³⁸

Publish full study details and data

As long as the private sector continues to control the funding, design, and analysis of most clinical research we need to aggressively push for the public availability of clinical trial data to allow for independent analysis. Although trial registers have been established in the US and the European Union, many postings do

not include results,^{39 40} and these repositories do not require the detailed information found in clinical study reports, which manufacturers submit to regulators in support of new drug approval.⁴¹ The FDA's finalisation of its enforcement procedure for clinicaltrials.gov reporting requirements should help in this regard.⁴² Drug and device companies' ability to hide unfavourable research results⁴³ would also be much reduced if regulatory authorities followed the lead of the European Medicines Agency and Health Canada and released clinical study reports with minimal redactions at the time of drug approval.⁴⁴ Even more useful would be access to all independent individual participant level data⁴⁵ along with protocols and analytic codes.

Most clinical trials are not accompanied by publicly accessible protocols, and compounding this problem,⁴⁶ discrepancies are often found between registered and published outcomes.⁴⁷ Journals could make a substantial contribution to correcting these problems by requiring manuscripts to be accompanied by published protocols, preferably peer reviewed, including any modifications to those protocols and ensuring authors address inconsistencies between protocols and publications.

Managing and avoiding conflicts of interest

The effects of conflicts of interest on the outcomes of clinical research can be reduced either by ensuring that they are fully declared and made public or, even better, eliminated by avoiding them from the outset.

Declared conflicts of interest are too often not acknowledged as being influential and are ignored or not taken into account in the transmission of research knowledge,^{48 49} and clinicians and other users of research often lack the training and knowledge to assess the likely effect of conflicts of interest on the integrity of reported research findings.⁵⁰

The US Physician Payments Sunshine Act of 2013 mandates that drug and medical device companies report any transfers of value to physicians of more than \$10.⁵¹ These reports are then compiled in the publicly available Open Payments database. Some European countries and Australia have adopted similar laws or their industry associations have agreed to provide similar information.^{52 53} However, this approach has limitations. As currently designed, open payments databases are not detailed enough to reveal the full extent of industry involvement in study design, implementation, and reporting.⁵⁴

Open payment databases need to be expanded to include researchers so that their conflicts of interests can also be probed. ProPublica has pioneered Dollars for Profs, a publicly searchable database showing the outside income and conflicts of interest of professors, researchers, and staff at US state universities and the National Institutes of Health.⁵⁵ At least one journal already publicly declares its income streams,⁵⁶ and this could become an accepted badge of quality, especially if accompanied by an annual report detailing efforts to move away from commercial sources of revenue.

Disclosure of interests is not sufficient to protect against commercial influence⁵⁷ so more needs to be done to avoid conflicts from the outset. Many academic researchers sit on the boards of drug companies while also serving on funding bodies, ethics committees, research steering groups, data safety monitoring committees, as heads of academic medical centres, and as editors of medical journals.⁵⁸ These links create an unacceptable conflict between commercial interests and the public interest and should not be permitted. When funding bodies and research ethics committees include people with commercial conflicts of interest they should be

required to explain publicly what steps were taken to find unconflicted people and why those efforts failed.

In addition, research institutions and academic medical centres should prohibit the more egregious interactions between faculty and drug and device manufacturers, such as serving on speakers' bureaus or being paid consultants. They should also outlaw any agreements that interfere in any way with their employees sharing data or publishing results of research. Beyond just enacting these bans, academic medical centres need to vigilantly enforce them, ensuring that staff are aware of all such policies⁵⁹ and sanctioning those who breach them. Aside from a few high profile instances,^{60 61} penalties for violating rules about conflict of interest appear to be rare.

Surveys of policies on conflicts of interest at academic medical centres, although slightly dated, have consistently shown substantial weaknesses in the areas covered and in the strength of the policies, including how they are enforced.⁶²⁻⁶⁴ We also recommend a national standard and international guidelines for such policies. If centres are lax in self-regulating or their policies are not broadly strong and uniform,^{18 19} there should be national policies for dealing with conflicts of interest, with institutions that do not comply being temporarily banned from public research funding as a deterrent.

Drug regulation

Nearly all regulatory agencies, including the FDA and EMA, are funded directly by industry user fees, raising concerns about real or perceived influence on regulatory decisions. Industry fees in the US accounted for about 80% of the salaries of review staff responsible for the approval of new drugs.⁶⁵ Almost 90% of EMA revenue comes from user fees.⁶⁶ Even though evidence of direct influence is not conclusive, we believe that drug regulatory agencies should be fully government funded to enhance public trust in regulatory functions. While working towards making regulatory agencies more independent, steps must be taken to ensure the independence of the data that regulators review. To this end we recommend that at least one pivotal trial should be conducted independent from the company submitting the application for approval.⁶⁷

Conclusion

The shape of the research agenda, the production of research, its subsequent interpretation, and dissemination, and its role in decisions about which drugs and devices reach the market are central to medical care that patients receive. Society has a duty to ensure that information is produced and disseminated fairly for the benefit of patients and public health. No single solution will eliminate commercial influence and bias from clinical research. The above proposals aim to accelerate a necessary shift in culture and practice that will ensure that research evidence is produced and disseminated more fairly. We welcome comments on these recommendations and additional suggestions for achieving greater independence from commercial influence.

Key messages

- The goal of clinical research should be to improve treatment that patients receive
- Clinical research in drugs and devices is often corrupted because of the involvement of commercial interests preventing it from achieving its potential
- We identify key sources of bias in clinical research and offer recommendations for minimising or eliminating them

Contributors and sources: All authors have substantial experience in examining biases in all phases of clinical research, including its conduct and how it is interpreted and communicated. In writing this article we drew on our collective knowledge of these issues along with previous literature on these topics that all of us have had a substantial role in producing. JL conceived the idea and wrote the first draft. JL, LAB, CD, and MAG gathered data, revised the manuscript for intellectual content, and approved the final manuscript. JL is the guarantor.

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