This is the author version of an article published as:


Access to the published version: http://dx.doi.org/10.1353/pbm.0.0082

Copyright: The Johns Hopkins University Press
Justice in health research: what is the role of evidence-based medicine?

Wendy Rogers¹ and Angela Ballantyne²

¹ Wendy A Rogers
Associate Professor, Medical Ethics and Health Law
Department of Medical Education
Flinders University
GPO Box 2100, Adelaide SA 5001
Tel: +61 8 8204 3132
Fax: + 61 8 8204 5675
Email: wendy.rogers@flinders.edu.au

² Angela Ballantyne (BSc, PhD)
Institution for Social and Policy Studies
Interdisciplinary Center for Bioethics
Yale University
PO Box 208209
New Haven, CT 06520-8029
Email: angela.ballantyne@yale.edu
Abstract

Evidence-based medicine (EBM) aims to facilitate access to up to date and accurate information about the effectiveness of medical interventions, in order to improve human health. The quality of the research results available for EBM processes of synthesis and meta-analysis is critical to this process. EBM is founded, more or less explicitly, on a vision of medical research in which curiosity driven investigators recruit altruistic citizens to participate in trials aimed at creating safe and effective therapeutic agents for the good of all. If there are distortions or corruptions in the research process, EBM becomes a false prophet, collecting and propagating unreliable results. In this paper we examine flaws in current processes of research production, the implications of these for justice and vulnerable patients, and explore possible solutions.
Introduction

The official ‘birth’ of evidence-based medicine (EBM) occurred in 1992 with the publication in the *Journal of the American Medical Association* of the paper by the McMaster evidence-based medicine working group (Evidence-Based Medicine Working Group 1992). In the years since then, EBM has attracted its fair share of controversy (Jenicek 2006). At its best, EBM seems to offer a vision of clarity in medical practice based upon the ideal of practitioners using the best available evidence as the foundation for informed decision making with patients (Strauss & Jones 2004). At its worst, EBM may represent a return to medical paternalism with experts prescribing algorithms for care in the form of clinical guidelines, taking little account of the many factors likely to render the guideline unreliable, biased or irrelevant to the specific patient needing care (Brase 2005). In between these two extremes, there lies a spectrum of views about EBM, together with ongoing debates about just what the contribution of EBM is, or has been, to improved patient outcomes (Buetow et al 2006). More recently, the activities of EBM have engaged the interest of ethicists, who have raised issues ranging from patient and clinician autonomy through to use or misuse of evidence in allocation decisions about health care resources (see for example Goodman 2003; ter Muelen et al 2005).

Much of the focus on EBM in the past sixteen years has been on finding and using evidence from clinical trials to make guidelines. Around the world, clinicians have struggled to master the techniques of searching literature and performing meta-analyses, and then struggled more with making sense of their results in terms of individual patient care. Partly in response to this, a whole industry of reviewers and guideline developers has sprung up, with academics and clinicians donating often astonishing amounts of time and energy to reviewing research for groups like the Cochrane Collaboration. Research is the foundation and the life blood of EBM, making it therefore, important to consider the ethical issues that arise in the production of research. Here we turn our attention to issues of justice arising from the research that underpins the reviews and the search for the best available evidence. We examine two aspects of medical research. First, we consider the production of research – (a) the constituents of research populations; and (b) the structure of the research agenda. Second, we discuss research results – access to and publication of results, and analysis of results by agencies such as the Food and Drug Administration (FDA) for drug approval, and by reviewers for EBM analysis.
Within each subsection, we investigate the impact of research distortions on the systematic reviews and clinical guidelines that are the practical outputs of EBM. Flawed research undermines the whole raison d’etre of EBM. EBM is founded, more or less explicitly, on a widely-shared vision of medical research in which curiosity driven investigators recruit altruistic citizens to participate in trials aimed at creating safe and effective therapeutic agents for the good of all. The key elements of this model are ethical research, integrity in research methods and publication of peer-reviewed results in the public domain. This process allows grouping and meta-analysis of multiple trial results, leading to stronger evidence about the safety and efficacy of treatments. Without good quality research, EBM becomes a false prophet, collecting and propagating unreliable results. Worse still, these distortions can perpetuate and exacerbate injustices in research and further marginalize vulnerable patients.

Throughout this critique we focus on research-related justice in EBM, in particular two sub-themes of justice - the role of industry and impacts on vulnerable populations. Before proceeding with our analysis, we should therefore explain what we mean by justice in health research and the role of EBM. In terms of medical practice, EBM is grounded in notions of non-maleficence and beneficence – that is providing safe and efficacious treatments that avoid harms and provide benefits to patients. The contribution of EBM to patient autonomy is more contentious and lies outside our present scope (see for example Hope 1996, Rogers 2002). As part of its role to inform practice, EBM aims to ensure that medical research is translated efficiently and accurately into clinical guidelines, thereby improving clinical care and health outcomes. The EBM project has not been directly concerned with how these improved health outcomes are distributed amongst the population, and therefore has not had a primary focus on justice in terms of equity of access to treatments or of health outcomes. Because however, EBM act as a ‘clearing house’ for research, issues of justice arising from the research that informs EBM can legitimately be considered amongst the ethical issues raised by EBM itself. For the purposes of the current analysis we take justice in research to include at least these three components:

1. fair access to research participation, with no exploitation of vulnerable groups nor unjustified exclusions of potential participants;
2. A just global research agenda that distributes health research resources fairly in relation to disease burdens. Developed countries have a justice obligation to spend some of their health research budgets on conditions affecting poor populations (London 2005); and

3. fair processes, such that research is designed and performed in ways to derive maximum utility from the results which are then presented in an unbiased and publicly accessible format, and that those reviewing research are not subject to financial conflicts of interest.

In summary, just research is that which contributes to identifying safe and effective treatments that reduce the global burden of disease. There is not space here to argue for these assumptions and claims; rather we present them as background premises to the ensuing analysis.

The production of research

There have been significant changes in the structure of research over the past 20 years. These relate to the funding of research, its location and the ways in which it is organised. These changes have put increasing power and control into industry hands, with consequences for the welfare of research participants and the integrity of the research itself. Given the importance of high quality research to EBM, these are serious issues.

The pharmaceutical industry is the greatest source of research funds on a global scale. The Global Forum in Health Research estimates that the private for-profit sector funds 48% of global research annually, investing approximately US$ 60.6 billion (World Health Organisation 2007). Their funding is increasingly channelled through contract research organisations (CROs) rather than academic institutions. Estimates suggest that, between 1992 and 2001, CROs increased their numbers of enrolled research participants from 7 to 20 million, with a commensurate increase in income from US$1.0 billion to $7.9 billion (Mirowski and Van Horne 2005, cited in Sismondo 2008). The market imperative requires CROs to be competitive, with pressures to contain costs and produce results.

Greater commercial control over research funding allows industry to play a larger role in research design and conduct. Industry has an obligation to its shareholders to make a profit, which creates significant incentives for introducing bias into the research process, as there is pressure to produce profitable results.
There are a number of ways that bias may be introduced into research. First, the design of the study may be manipulated to produce positive results. The choice of comparator (for example placebo or sub-optimal dose of competitor drug) can make a positive finding more likely, as can the selection of participants who may have characteristics that favour the drug under investigation. Second, outcomes may be selected to favour the trial drug, or the statistical methods used may minimise or mask adverse events. Recent investigations have demonstrated a clear association between funding source and trial outcome, with commercially funded research three to four times more likely to have findings favourable to the sponsor than non-industry funded research (De Vries and Lemmens 2006).

The structure of research has profound implications for the quality and integrity of the evidence base that underpins EBM. In the next sections, we discuss the selection of participants in research and setting the research agenda in more depth. These activities have both changed as a result of the commercialisation of research, with consequences for disadvantaged groups and the ideal of scientifically sound evidence informing practice.

**Participants in research**

The question of who to involve in research is a vexed one. On the one hand, the more specific the question and the more homogenous the research population, the more likely a trial is to produce a definitive answer. This leads to a search for research participants with single conditions and minimal variables. On the other hand, the results of trials have to be “applied” to diverse populations, comprised of women and men of multiple ethnicities and with variable co-morbidities. Research with representative populations is necessary to develop medical and clinical knowledge about the aetiology of disease, and the safety and efficacy of medical interventions in diverse populations (Rogers 2004).

Commercial pressures lead to demands for fast answers, making the narrowly focused trial with homogenous participants appealing, as this will answer the question most swiftly. This however, leads to a number of injustices. Certain populations may be overburdened with research because they are accessible, compliant or financially needy. Elliott (2008) has described vividly the lives of those who ‘guinea pig’ for CROs in the US: it is a far cry from the ethical ideal of research participation as detailed in the Nuremberg
code or the Declaration of Helsinki. Given the sometimes appalling conditions in which US citizens contribute to the research endeavour, it is unlikely that conditions are better for people in Asia and Eastern Europe, who are becoming the participants of choice for commercial medical research (Petryna 2007).

Conversely, questions of justice also arise when potentially vulnerable populations are excluded from research. The systematic exclusion of women and minority groups from clinical research in the 1970s-1990s has been well documented (Dresser 1992). The exclusion of women from landmark research studies such as the Multiple Risk Factor Intervention Trials (known as MR FIT) and The Physician's Health Study generated significant concern and international debate (GAO 1990). In response, many countries introduced guidelines, regulation, and in the case of the National Institutes of Health (USA), legislation requiring researchers to include both women and ethnic minorities in research.

Three related factors were responsible for the under-representation in clinical research of women, ethnic minorities and other groups perceived to be ‘vulnerable’, such as children and prisoners: explicit protectionist policies of exclusion; practical considerations of research efficiency and cost; and false assumptions about the relevance of sex, gender and racial differences.

The protectionist policies of the 1970s were in fact a backlash against previous exploitation of vulnerable populations in research. The 20th century contained a number of examples of blatantly unethical research with vulnerable populations, including the Nazi World War II medical experiments conducted on concentration camp prisoners; and the Tuskegee syphilis study conducted in Alabama (USA) between 1932 and 1972 (Thomas and Quinn, 1991; Caplan 1992). Public protest led to the development of medical research guidelines such as the 1949 Nuremberg Code of medical research, and the US 1979 Belmont report. These, along with guidelines in other jurisdictions, focused on informed consent, preventing exploitation, and just subject selection. They ushered in a protectionist research paradigm in which researchers conservatively sought to avoid exploitation by recruiting non-vulnerable research populations – middle-aged, white, males. For example, from 1977 to 1993 the Federal Drug Administration (FDA) in the United States prohibited research including women of childbearing potential in early phase drugs trials to avoid potential harm to reproductive capacity or their fetus if they became pregnant (Merkatz et al 1993).
There were purported practical reasons for the exclusion of women and minorities from research: the alleged need for homogenous populations, the cost of including minorities and women, and the difficulty of recruiting these populations (Dresser 1992; Ferguson 2002). These justifications reflect what we call the ‘distortion paradigm’, which defines the white adult male body as normal and considers female biological processes as distortions of this norm. Interestingly and paradoxically, biological processes were thought to interfere with research to a sufficient degree to justify the exclusion of women, minorities and children, and yet these groups were thought to be homogeneous enough such that research results from predominantly white, adult, male studies could be used as the basis of guidelines for the general population.

Despite regulatory efforts to encourage the inclusion of women and minorities as participants in research some distortions still exist. Unfortunately, recent evidence demonstrates the persistent under-representation of women over the age of 65 in research and the over-representation of men in studies of heart disease and colorectal and lung cancer trials (Murthy 2004; Hutchins 1999).

The overall effect of these practices in selecting ‘suitable’ research participants is the production of research results that are unable to answer questions about safety and efficacy for many of the end users of the research products. Given that EBM is built on meta-analysis and reviews of the best available research, the resulting guidelines will only be as good as the quality of research from which they are derived. Despite increasing recognition of sex and gender differences in cardiovascular disease (CHD) in the scientific and medical literature, a recent review has demonstrated that most contemporary guidelines for prevention, diagnostic testing and medical and surgical treatments for cardiovascular disease are still based on studies conducted predominately on middle-aged men (Wenger 2006).

In the absence of research including women, minorities and children, clinical treatment is based on studies with adult male research populations, despite important physiological differences between ethnicities, men and women and between adults and children. This extrapolation can lead to both the under-treatment of some populations, such as pregnant women and children, because there is a lack of clinical data demonstrating safe and effective treatment options, and exposure to harm from unknown risks of drugs in
these populations (Rogers 2004). The ethical issues associated with the inclusion of children and pregnant women in research are particularly vexed. Yet, pregnant women and children require medical treatment and the choice is thus between exposing them to potential harm in a regulated and monitored research setting, or exposing them to potential harm in an unmonitored clinical settings through withholding treatment or through provision of treatment untested in these populations.

It is apparent that groups traditionally excluded from research, such as women and some ethnic groups, continue to receive sub-optimal clinical care. Women have not, for example, achieved the same gains in relation to coronary heart disease (CHD) as men: despite significant improvements for men, mortality from CHD in women has not declined in the past 20 years (American Heart Association 2006). The relationship between historical exclusion from research and current under-treatment represents a correlation rather than a demonstrable causal link. Nevertheless, it seems clear that EBM cannot deliver safe and efficacious treatments for women, minorities and other disadvantaged groups without appropriate research evidence that includes fair representation of these groups.

**Improving participation in research**

Effectively regulating the participation in research of previously excluded and/or vulnerable groups is a challenging problem. To date, the American regulation of the inclusion of women and minorities in NIH funded research (*National Institutes of Health Revitalization Act* 1993) represents the most sophisticated international model. The NIH Inclusion Policy is backed by strong financial incentives as the success of NIH grant applications is dependant on satisfactory targets for the recruitment of women and minorities, with targets reviewed by specialist scientific peer-review committees. Funding can be withdrawn from a project if recruitment does not match agreed inclusion targets. There is some evidence that the NIH guidelines have an indirect impact on research outside of America, with chairs of Human Research Ethics Committees in Australia commenting that Australian research projects receiving NIH funding or involving American collaborators are more likely explicitly to disclose the numbers of women recruited for the research (Ballantyne and Rogers 2008). Countries such as Canada and Australia may well need more robust regulation of research to ensure that women and diverse ethnic groups are appropriately represented.

Inclusion guidelines should be tied to public research funding and suitably qualified scientific peer-review.
These regulations cannot easily be extended to apply to privately sponsored research. Other universal mechanisms such as Institutional Review Boards (IRBs) and FDA approval of trials apply to commercial research sponsors. However the effectiveness of these instruments has also been criticised: now that many drug studies occur outside of academia, sponsors can shop around for a favourable for-profit IRB who will promise fast approval (Elliot 2008); we discuss concerns about conflict of interest amongst FDA reviewers below.

Improving participation in research of traditionally excluded groups does not always entail ‘equal’ participation. Research protocols must: be informed by an investigation of the theoretical likelihood of differences between subgroups; be designed to detect any differences between subgroups; and include appropriate statistical sub-group analyses to look specifically for the effects of sex, gender, age, race and so forth.

**The research agenda**

The research agenda determines what research is conducted and therefore which results will be available to inform EBM. With global health research funding fairly evenly split between private-for-profit sector sponsors (48%) and public sector sponsors (45%), the research agenda reflects a mix of the interests of industry and the governments of predominantly high-income countries. The role played by commercial research sponsors has increased over recent decades, leading to a stronger focus on patentable treatments that address the needs of affluent markets. As a result, there is under-funding of diseases of poverty, of epidemiological research, and of research into non-patentable behavioural and environmental solutions to ill-health (Trouiller et al 2002). To be explicit, the problem here is twofold – first an emphasis on patentable treatments (for example drugs) at the expense of other potentially effective but less-profitable interventions; and second a focus on conditions prevalent in rich populations. We deal with each of these in turn.

This focus on drug research is compounded by the dominance of the randomised control trial (RCT) in EBM. In a ‘happy accident’, the interests of industry in developing patentable treatments align well with the reliance of EBM upon the RCT, just because drugs happen to be especially suited to testing in an RCT. The goals of commercial research sponsors, combined with the methodological standards of EBM, create an
increasing emphasis on pharmaceutical solutions to disease. The clinical evidence base is dominated by RCTs of drug treatments. This in turn impacts upon the shape of medical practice as a whole. When a clinician asks, “What is the best treatment for raised cholesterol?” the answer will come back loud and clear that published studies support the effectiveness of statins. We do not know what other effective interventions may have been identified had the research agenda (with funding to match) had less of a focus upon RCTs of potentially profitable drugs. Furthermore, in many countries, it is the public purse that supports purchase of medications. By providing the evidence that EBM requires - results from RCTs - industry can influence not only clinicians but also government purchasing authorities. Given that up to 70% of premature death in the United States is estimated to be caused by environmental and behavioral factors (Lee and Paxman 1997), a narrow focus on drug development can never maximize population health outcomes. Expanded research in social and environmental health innovation is needed to balance out the research agenda.

Patents provide financial incentives that direct research towards drugs with a profitable market, regardless of whether the drugs address significant disease burdens. As we know, the private for-profit sector is the largest investor in health research globally. Predictably, the majority of global expenditure on health research is directed towards conditions of the wealthy, which account for only a small percentage of global morbidity and mortality; while conditions afflicting the majority of the world’s poor remain under-researched. Industry will invest in Viagra rather than vaccines, if Viagra promises a greater return on investment.

Does this approach to research meet the requirements of justice in research as we have framed them? A just research agenda would address the health needs of all populations, and work to minimise the global burden of disease. National funding bodies have the capacity to set national research priorities and allocate funding for projects addressing these questions, however governments cannot dictate to private industry where they should invest their research dollars. In a free market democracy, private enterprise has the right to research and develop whatever products it so chooses. However, as governments around the world recognise, healthcare is a special good because of the strategic importance of health to an individual’s opportunity range and her ability to fulfil her life goals (Daniels 1985). Health research is more complex than just
turning a profit. The current reliance on commercial sponsorship of research cannot fulfill the requirements of a just research agenda because it does not support the distribution of safe and effective medical interventions for the global poor. We now discuss strategies for curbing the influence, and minimizing the distorting practices, of industry.

**Changing the direction of the research agenda**

In addition to the patent system, it is clear that alternative mechanisms are required to enhance innovation, research and development for diseases predominantly affecting poor populations, thereby moving towards justice in the research agenda. Numerous models have been suggested and are currently being debated. Philosopher Thomas Pogge has, for example, suggested a parallel patent system, where inventors could opt to apply for a ‘health impact’ patent where their financial return is calculated according to the impact of their intervention on global morbidity and mortality. An alternative approach is that of the proposed Medical Research and Development Treaty, which would determine global research priority areas and signatories would agree to invest a set proportion of their GDP in funding priority research projects. These strategies are ambitious and promising, but unlikely to be implemented in the near future.

Other approaches, more limited but also more immediate, to setting the research agenda include community-based participatory research (CBPR) which aims to improve the correlation between health research and community health needs. This approach ensures that the target consumers of research knowledge are actively involved in setting the research agenda and designing research protocols. Models of effective CBPR have been demonstrated in research with traditionally underserved groups such as indigenous populations and drug users.

**Ownership, publication, and review of research results**

We have already commented on some of the effects of the commercialisation of research and the increasing use of CROs to perform research for pharmaceutical companies. There is one final consequence flowing from the emergence of CROs that we need to consider, and that relates to ownership and control of the results of research. In academic settings, there is an imperative to publish. Ideally, the motive for this is to make results public, in order to advance knowledge, and ultimately to benefit patients. There are ancillary
benefits for academics, as publications are widely recognised as a sign of success and are increasingly a requirement for career progression. CROs however, are free to protect the interests of their funders by engaging in a number of publication practices that subvert the ideal of honest or unbiased communication for the public good. These practices have been described by others, most comprehensively Healy and Cattell (2003) and Elliott (2004). The process of publication planning in CROs involves hiring authors to ghost write manuscripts based on trial results, and offering these to established academics. In an apparent win-win situation, the academic secures a gift publication while simultaneously the addition of their name helps with securing publication in a prestigious journal (De Vries and Lemmens 2006). The links are not overt; a careful reading of the published paper may fail to reveal any ties with the pharmaceutical company or the CRO. But this is only the beginning. The publication campaign may be closely choreographed to flood the literature with accounts of trials favourable to the company’s interests. The sertraline campaign has been documented by Healy and Cattell (2003): 55 papers were organised by a commercial agency and published in the literature between 1998 and 2001. These became a significant part of the evidence base about sertraline, drowning out other more critical results published in less prestigious journals or with lesser known authors. Once this over-publication of positive results is coupled with suppression of unfavourable results, the literature, and thus the evidence base, then reflects a very partial and biased picture of the benefits and harms of particular drugs. Obtaining the unadorned results (both positive and negative) of trial results held by commercial companies can be a difficult if not impossible task. Manipulation of results in the public record skews the evidence, making the systematic reviews upon which EBM depends less than reliable.

The whole thrust of commercially funded research is to get new treatments to market as soon as possible. Regulatory bodies such as the US FDA are charged with approving new drugs, thus opening the gateway to the market. The FDA relies upon advisory committees to examine the research evidence provided by sponsors to investigate whether the drug is safe and effective, where ‘safe’ is understood to involve a balance between benefits and risks. Ideally this process should involve only those people who are free from conflicts of interest caused by industry links. Conflicts of interest lead to unpredictable bias, making the judgement of those concerned less reliable than it might otherwise have been. However, the reach of industry sponsorship means that it is increasingly difficult for the FDA to find experts without industry ties,
and hence a conflict of interest. In their study of FDA decisions, Lurie et al (2006) found that there was at least one advisory committee member with at least one financial conflict at 73% of meetings. Traditional approaches to conflicts of interest in this situation require disclosure and/or recusal, but disclosure of even quite substantial financial ties rarely led to recusal from specific meetings. The bias caused by conflicts of interest can be unpredictable: a biased decision maker may over or under-compensate for their bias. In the case of the FDA however, the bias seems to have worked in favour of industry. The authors calculated that for every one committee member with a conflict, there was a 10% greater likelihood that the meeting would favour the drug under review. Quantifying the effects of conflicts of interest is a challenging task; nevertheless, it seems reasonable to assume that if this level of bias exists at the FDA, despite its formal procedures for disclosure, the biases are likely to be equal or greater in researchers performing and reviewing research of commercial funders.

One solution would be to use only those academics and specialists without conflicts of interest, but this is problematic: in a 2002 editorial, Drazen and Curfman of the *New England Journal of Medicine* announced a change in their conflict of interest policy for authors of review articles and editorials. For these types of articles, the journal would now exclude only authors with a ‘significant financial conflict-of-interest’ whereas it had, prior to 2002, excluded any author with a financial conflict of interest. The journal justified its change in policy by citing the difficulty they had had in finding authoritative specialists *without* a conflict of interest (Drazen and Curfman 2002).

The final outcome is the creation of a research literature base that is very much shaped by the interests of industry, rather than by concern for patient welfare, global disease burden or independent academic activity.

*Improving access to research results*

There are various mechanisms for improving the transparency of clinical research, publication of results and the accountability of researchers. In 2005, the International Committee of Medical Journal Editors (ICMJE) circulated a policy requiring researchers to register their trial design in an approved and publicly accessible clinical trials registry (CTR), before the onset of patient enrolment, as a condition of publication of trial results in the world’s leading medical journals (International Committee of Medical Journal Editors
Clinical trials registries are designed to combat selective reporting of trials, a practice which distorts the body of evidence available for clinical decision making. Despite initial resistance from the research community, CTRs have been an overwhelming success. There are five CTRs that meet the ICMJE criteria, and the largest - ClinicalTrials.gov in the US – had over 54,036 trials registered in April 2008 and receives 40 million viewers per month (ICMJE 2005). Advocates are now calling for basic results reporting to be included in the CTRs. ICMJE will not count brief (<500 word) results reports as prior publication and this will therefore not impede publication of research results in journals (Laing 2007). Results reporting would further increase public transparency and would remove the monopoly the medical journals currently have over access to trial results. We recommend that CTRs collect fuller demographic data on the sex and ethnicity of participants to facilitate meta-analysis of the effectiveness of fair inclusion policies (Rogers and Ballantyne 2008). Implementing these proposals will allow the current research agenda to become more visible, making it easier for regulators to implement appropriate guidelines to improve fair participation within research populations, and for not-for-profit sponsors to direct research funds to diseases and conditions neglected by industry.

**Conclusion**

We have identified three main challenges to the current system for producing valid, reliable and just research. First, much of the research available for meta-analysis under-represents women (particularly pregnant women), ethnic minorities and children, thereby potentially excluding them from the benefits of safe and effective treatments. Second, the current research agenda is disproportionally driven by financial gain rather than a commitment to reduce morbidity and mortality, due in no small part to our heavy reliance on patents to drive medical innovation. Third, pharmaceutical companies and CROs orchestrate the dissemination of research results (through ghost-writing and targeted publication) to dominate and bias the medical and scientific literature. Industry ties to academics and specialists make it increasingly difficult for both journals and national regulatory bodies to find independent reviewers to assess research results.

The consequences of this approach to research and development is a skewing of medical research towards products that are likely to produce a profit, but may be of questionable safety and efficacy and may do little
to address injustices in the research agenda. EBM is inevitably caught up in this process as it is the mechanism whereby research results become translated into authoritative clinical guidelines and purchasing decisions. The ideal of EBM is to use the best possible information to guide clinical care, but as we have argued, the well is contaminated. If the published research base, which provides the data for EBM, is unreliable, skewed, and unjust in its goals and exclusions, then EBM can do little more than perpetuate these biases and unreliability. Worse still, the academic veneer and authority of EBM provide a mechanism for transporting the biased results of industry-driven research to the lofty altitudes of evidence-based guidelines.

The quality of EBM systematic reviews and clinical guidelines depends on the in-put. This is not simply a concern with the scientific validity of research, but is also a question of justice. Does the EBM process contribute to making safe and effective medicines accessible to all populations; or does it provide a legitimate veneer to a biased research literature based on un-representative research, and in doing so, perpetuate the marginalisation of vulnerable populations? We suggest that the latter is currently a more accurate characterisation.

There seem to be limited strategies for directing or controlling for-profit-research. As private companies in a competitive capitalist system, pharmaceutical companies and CROs are structured to prioritise profits over public health. In our view, the correct response to this situation is not simply to criticize incentive structures. The broader community has an obligation to establish mechanisms such as public funding of research that balance out the interests of private sector research, and structures such as CTRs that limit the ability of industry to distort the research literature.

In recent years we have relied ever more heavily on commercial sponsorship of research. To ensure a just research agenda that responds to the health needs of diverse populations (male and female, young and old, rich and poor) we require public investment in research. These funds need to be regulated in a manner that ensures just representation of sub-populations, and targeted at conditions neglected by the private sector.
When we have more confidence in the research base, EBM will be a valuable instrument for managing research and gleaning clinically useful guidance from its results. The ideal of EBM is to inform us about what is currently known about clinically effective treatments, and to avoid using ineffective or harmful treatments. This is a worthy ideal that should not be abandoned. But given the current biases in research, we need new ways of realising the ideal. The challenges include establishing what the ‘best evidence’ is for interventions that are not amenable to RCTs; determining the best methods for investigating differences between sub-groups; and supporting initiatives to improve the quality of published research. Some of the responsibilities lie with researchers: greater integrity would lead to researchers refusing funding for redundant and biased research or gift authorships, and seeking their rewards in performing research that makes a substantial contribution to improving global health. At present EBM is part of the problem, but it could equally be part of the solution.

Acknowledgements

The authors would like to thank Olga Anikeeva for research assistance, Jenny Doust and Ryan Orange for helpful comments on earlier drafts of this paper, and the reviewers for their insights.
REFERENCES


GAO Testimony: National Institutes of Health: problems in implementing policy on women in study populations. 1990. (GAO/T-HRD-90-38.)


Washington, D.C.