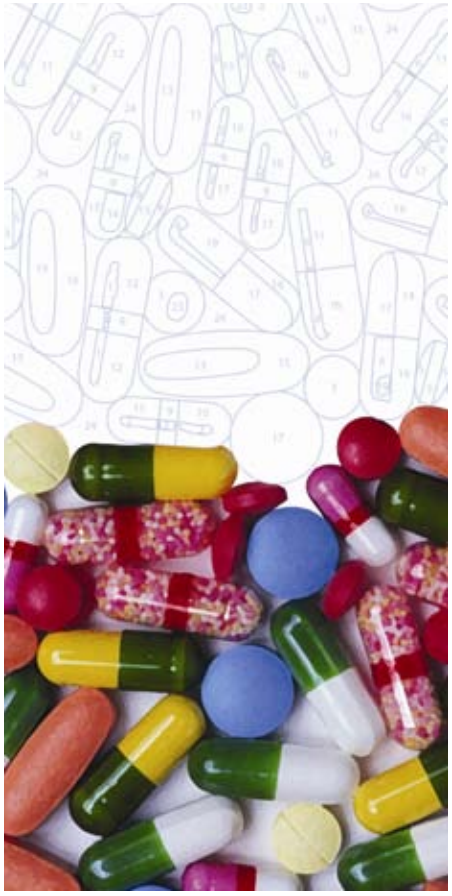
Are clinical trial data shared sufficiently today?

The AllTrials campaign asks for all trials to be registered and their results published. **John Castellani** thinks mandatory disclosure could affect patient privacy, stifle discovery, and allow competitors or unscrupulous actors to use the information. **Ben Goldacre** says we need the evidence to make informed decisions about medicines



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YES

Clinical trials are essential for the successful development of new medicines that save and improve lives and provide hope for millions of patients. Biopharmaceutical companies are committed to the continuous improvement of clinical trials to bring innovative medicines to the patients who need them. This includes protecting the safety of study participants, overcoming barriers to greater participation, and fostering new medical discoveries.

The biopharmaceutical industry is firmly committed to enhancing public health through responsible reporting and publication of clinical research and safety information. In the process of drug development, companies routinely publish their research, collaborate with academic researchers, and disclose clinical trial information at the time of patient registration, drug approval, and for medicines whose research programmes have been discontinued. In addition, PhRMA has set out voluntary principles to fortify biopharmaceutical companies' commitment to the highest standards for ethics and transparency in the conduct of clinical trials. PhRMA's *Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results*[1] are designed to help ensure that clinical research conducted by biopharmaceutical research companies continues to protect patients and provide meaningful medical research results to healthcare professionals and patients.

The biopharmaceutical sector may provide more information about its research and products than any other industry. As expected by the healthcare professionals that prescribe innovative medicines, the current biomedical research system includes wide sharing of trial results with government regulators, academic and medical communities, and physicians through submissions to the US Food and Drug Administration (FDA) and other international regulatory bodies, presentations at medical conferences, and publication in peer reviewed journals.

Information on clinical trials for potential new medicines is already required by US law to be posted on ClinicalTrials.gov, the publicly accessible clearing house maintained by the National Institutes of Health. As of May 2013, ClinicalTrials.gov has information on 146 213 studies in all 50 states and in 185 countries.

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NO

When discussing transparency, it is important to be clear what is being requested. At stake are four levels of information about trials: knowledge that a trial has been conducted, from a clinical trials register; a brief summary of a trial's results, in an academic journal article or regulatory summary; longer details about the trial's methods and results, from a clinical study report where available; individual patient data. The AllTrials campaign calls only for the first three to be published.

The most up to date review estimates that around half of all trials for the treatments being used today have gone unpublished, and that trials with positive results are twice as likely to be disseminated.[1]

In 2005, journal editors passed regulations stating that they would publish only registered trials: the evidence now shows that these regulations have been widely ignored.[2] In 2007, US legislation was passed requiring all trials since 2008 to post results on clinicaltrials.gov within a year of completion: the best published evidence shows this law has been ignored by 60-90% of trials.[3] If industry representatives believe these problems have been fixed, they should present published evidence to support their case. Even if the latest rules on transparency were to be implemented perfectly—starting from now—they would still do nothing to improve the evidence base for the treatments we use today, because they all cover only trials from the past few years. More than 80% of the medicines prescribed this year were generic, and came on the market more than a decade ago. We need the results of trials on these treatments, which are still available, albeit on paper.

The arguments against this level of transparency are conflicted and misguided. John Castellani, of the Pharmaceutical Research and Manufacturers of America (PhRMA), has claimed previously that it is enough for regulators alone to see all the information on trials, and to see it behind closed doors. But this goes against the fundamental principles of science: we rely on transparency about methods and results, so that every experiment can be double checked and critically appraised. Although he might not realise it, Castellani's position also exposes patients to real and unnecessary risks. Many of the most notable recent problems with medicines—problems with rofecoxib (Vioxx) and rosiglitazone (Avandia), for example, and problems with the evidence base for oseltamivir (Tamiflu)—were spotted by independent academics and doctors, and not by regulators.

The problem of withheld trial results has been documented since at least 1986,[4] and industry

The National Institutes of Health reported last year that ClinicalTrials.gov "receives more than 95 million page views per month and 60 000 unique visitors daily."[2]

While these efforts are working, the biopharmaceutical industry is engaged in a dynamic ongoing process to improve on all aspects of clinical trials and is committed to taking part in a multi-stakeholder dialogue to advance responsible data sharing that protects patient privacy, maintains the integrity of the regulatory review process, and preserves incentives for biomedical research. We are reaching out to groups such as the Institute of Medicine, the Harvard Multi-Regional Clinical Trials Center, Project Data Sphere of the CEO Roundtable on Cancer, and the European Alliance for Personalised Medicine.

Processes for data sharing or disclosure must take account of patients' informed consent and the reality that re-identification of patients based on anonymised information is possible.[3] Threats to patient privacy will jeopardise patient willingness to participate in clinical trials, which would delay the availability of new therapies.

Dumping millions of pages of clinical trial information into the public domain without providing appropriate scientific and clinical context or guidelines for meta-analysis could lead to second guessing of the expert decisions of national regulators worldwide, undermining patient trust and confidence in the safety and effectiveness of approved medicines.

Mandatory public disclosure of intellectual property, confidential commercial information, and proprietary scientific methods found in clinical trials could stifle discovery and open the possibility of competitors or unscrupulous actors using the information for their own products in other markets or countries. Without appropriate protection for intellectual property to incentivise the enormous investment risk involved, biopharmaceutical companies will be discouraged from investing in the next generation of new medicines, leading to patients and physicians being deprived of innovative therapies to tackle the serious and life threatening diseases of the 21st century.

The modern clinical trial system and associated sharing of information led to more than 340 new medicines being approved by the FDA over the past decade, with 39 new medicines in 2012 alone. It contributed to over 30 new medicines approved for HIV in the past three decades—based on the work of 2400 completed trials—turning what was once a death sentence into a treatable, chronic condition.

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Since 2000, PhRMA member companies have invested about $550bn (£330bn) in research and development, including clinical trials, in the search for new treatments and cures. No government or academic institution has the resources or multidisciplinary expertise to conduct the clinical trials needed to develop the new medicines patients need. Only the biopharmaceutical industry can take on this considerable risk on such a scale, and only a carefully balanced regulatory and competitive environment can foster the future investments in this research necessary to produce new treatments to benefit current and future patients.

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The problem of missing trials is one of the greatest ethical and practical problems facing medicine today

has successfully delayed remedial efforts for three decades. The latest strategy has been to raise the spectre of patient privacy.

In February, for example, PhRMA released a colourful statement that misleadingly suggested that I and the *BMJ* had somehow called for the reckless public release of full individual patient datasets. This is despite the fact that the head of press relations at PhRMA already knew that neither I nor the AllTrials campaign call for individual patient data to be published.[5 6]

The *BMJ* has recently called for individual patient data to be made more widely available, in an editorial.[7]

Was this reckless and unreasonable? I don't believe so. In many fields, there is already a long history of sensible and cautious sharing of detailed datasets—for example, to conduct individual patient data meta-analyses. These produce better estimates of treatment benefits, and improve care for patients, with appropriate concern for confidentiality. The Early Breast Cancer Trialists Collaborative Group's meta-analyses, already published, represent just one notable example.[8] The YODA project at Yale is looking at best practice for data sharing, as are many other groups.[9] What's more, the European Medicines Agency (EMA) has fully committed to sharing individual patient data after 2014.[10]

Is patient confidentiality also an issue when clinical study reports are shared, as AllTrials and I have suggested they should be? Clinical study reports are long documents—often thousands of pages—but they are important, because analyses have shown that the information published in academic journal reports on clinical trials can be misleading or inaccurate, when compared with these longer, definitive sources of information.[11 12]

These reports certainly do contain some information about individuals—for example, in narrative descriptions of adverse events—but such information can easily be removed, or shared only with named researchers, if this is deemed necessary. Some industry figures have claimed that removing this material is either impossible or prohibitively expensive. But in 2010 the European ombudsman made a ruling of maladministration against the EMA, for claiming exactly that. Since then, the agency has released 1.6 million pages of clinical study reports.[14]

This campaign has rapidly snowballed to become the mainstream position in the United Kingdom. AllTrials is now supported by more than 50 000 individuals, and 250 organisations, including more than 100 patient groups, the National Institute for Health and Care Excellence, academic funders such as the Medical Research Council and the Wellcome Trust, royal colleges, the Royal Pharmaceutical Society, the British Pharmacological Society, and the Faculty of Pharmaceutical Medicine, to name but a few. Ironically, within 24 hours of PhRMA denouncing our calls for greater transparency, GlaxoSmithKline—the world's fourth largest drug company—signed up as a supporter of alltrials.net.

If the transparency we ask for is practical, and reasonable, then what lies behind the colourful denunciations of PhRMA?

The problem of missing trials is one of the greatest ethical and practical problems facing medicine today. It also represents a bizarre paradox: we can spend millions of dollars on a trial, hoping it is free from bias, trying to detect a modest difference between two treatment groups; and then at the final moment we let all those biases and errors back in, by permitting half the results to disappear.

Competing interests: I am a doctor, academic, and writer. I make income from talking and writing about problems in science, including publication bias. My research fellowship in epidemiology is funded by the Wellcome Trust, a signatory to AllTrials.

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