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Shining a light on trial data

The European Medicines Agency's request to make all clinical trial data available is key to countering bias in publication, drug prescription practice and health policy.

In mid-April, a powerful group of European drug regulators called for clinical study reports—the raw data from clinical trials—to be made publicly available. Writing in the open-access journal *PLoS Medicine* (**9**, e1001202, 2012), the heads of the Dutch, French and UK drug regulators, together with the head of the European Medicines Agency (EMA), make the important positioning statement that clinical trial data should not be considered commercially confidential information. They argue that "most patients enrolling in clinical trials do so with an assumption of contributing to medical knowledge, and 'non-disclosure of complete trial results undermines the philanthropy'."

The regulators' call came, at least in part, in response to another submission to *PLoS Medicine* (**9**, e1001201, 2012) from three independent researchers undertaking a Cochrane review—the gold standard reports for guiding clinical practice—of an approved drug, Hoffmann-La Roche's influenza virus neuraminidase inhibitor, Tamiflu.

Tamiflu was heavily promoted by Roche and then broadly adopted and stockpiled by several European governments, the United States and the World Health Organization as a public health defense against the bird flu epidemic. The rationale was that it would protect influenza-infected patients from severe complications and deaths associated with disease. The rise of Tamiflu thus owes much to the endorsement of this rationale by major and influential government agencies.

The question is whether the claims that the drug can address influenza complications or suppress virus transmission are correct. And it is this question that three independent groups of researchers tried to answer by looking at the trials that Roche undertook on Tamiflu which formed the basis for the drug's US Food and Drug Administration (FDA)'s approval in 1999, the implications of which had not been made clear in any of the many journal articles that Roche and its collaborators had published. Importantly, when it approved Tamiflu, the agency did not allow Roche to claim either effectiveness in dampening influenza complication or in blocking transmission.

When the researchers set about seeking access to these data, they hit a roadblock in the form of Roche. Some of the details of Roche's procrastination and obfuscation can be found in the *PLoS Medicine* paper, and need not be relisted here. In response to these findings, the European regulators lay out several reasons why clinical study data should be made much more widely accessible. They point out, for instance, that raw clinical data might enable the development of predictive models for orienting patients to appropriate treatments. They are also realistic enough to recognize that there are perfectly good reasons why raw clinical data has to be treated with care. There is, for instance, the narrow objection that patient confidentiality must be respected. They also suggest that analysis of raw data by 'independent' researchers is not in itself a conflict of interest–free zone. Another concern is that smaller companies with experimental therapeutics in early human testing have a lot to lose if early clinical data were made available—larger companies with deeper pockets could capitalize by pushing competing programs faster through trials and to market.

Ultimately, though, the authors make a persuasive appeal for more open access to clinical data: "...in an open society, trial sponsors and regulators do not have a monopoly on analyzing and assessing drug trial results." In other words, although companies and agencies have their jobs to do, the checks and balances that societies need to have cannot rest entirely on the trust placed in either the regulators or the pharmaceutical industry.

This is a highly commendable sentiment. The problem is that it is almost in direct opposition to the way in which drug regulation has evolved during the past two decades.

The regulatory process is frequently recursive—indicating that the ground rules are not that clear, even to those in the know. Regulatory decisions often apparently *surprise* companies, although this can sometimes be put down to a level of self-delusion, especially in companies where all is riding on one trial. And most important of all, regulators sometimes disagree with each other—see, for example, the contrasting decisions of the EMA's advisors and the FDA this year for the diabetes drug dapagliflozin.

The lack of transparency in drug development is not helped by the size and complexity of the submissions that drug companies make and which regulators require. It could also be argued that regulators and companies alike have contributed to a system that not only places a considerable financial burden on drug developers but also serves to promote among commercial concerns a feeling of righteous indignation with respect to data ownership and perhaps to make regulators their protective allies.

It is hard to believe that the regulators and pharma companies can untangle their mess themselves. But there is hope in the growing power of those who most contribute to the success of clinical research and who also stand to benefit the most from successful outcomes of drug development: the patients. If patients imposed their will on the process more forcibly—perhaps by signing only consent documents that committed companies to making sure that data obtained from experiments on their bodies were used as widely as possible—then companies and regulator might more quickly be persuaded to do the right thing.

This journal wholeheartedly endorses the EMA's position that raw data should be openly available with all the necessary protections for commercial confidentiality and the personal privacy that it entails. Tamiflu is not the first drug for which previously unpublished, detailed clinical trial data have radically changed public knowledge of safety and efficacy—others include Avandia, Neurontin and Vioxx. Shining a light on all the data about a drug is the best antidote to bias in clinical research reporting. It is in the interests of researchers, patients and healthcare payors. And ultimately—if only the companies would see it—it would boost the industry's reputation as well.