nature medicine

The sounds of silence

On June 2, New York State Attorney General Eliot Spitzer sued GlaxoSmithKline (GSK) for repeated and persistent fraud, contending that the company failed to disclose information on the safety and efficacy of paroxetine for the treatment of depression in children. This lawsuit quickly prompted appeals from several quarters for increased transparency in the publication of clinical trial results, particularly negative data. Although this idea has received widespread support, its implementation is likely to be fraught with challenges.

The idea is that companies, journals and scientists tend to showcase only positive results, sweeping negative data under the carpet. Making negative results as visible as positive findings, the argument goes, will enable doctors to make more informed decisions about which medicines to prescribe to their patients.

At the center of the dispute is the allegation that GSK withheld data from several trials indicating that paroxetine was ineffective in treating depression in children and adolescents and might increase the risk of suicide in depressed teenagers. In May 2003, the UK Medicines and Healthcare Products Regulatory Agency became aware of these data as GSK sought approval to treat obsessive-compulsive disorder with paroxetine, and the agency banned the drug's use in people under 18. Shortly thereafter, the US Food and Drug Administration (FDA) issued similar advice to doctors (see News, page 655).

Not unexpectedly, GSK has denied wrongdoing. Other companies, such as Abbott, Pfizer and Merck, promptly stated their commitment to the principle of releasing trial results, regardless of the conclusion, and their disapproval of suppressing the publication of negative studies.

While the legal battle unfolds, different groups have pointed to the need for better ways to publicize the results of every clinical trial. A 6 June editorial in *The New York Times* advocates forcing pharmaceutical companies to publish the results of their trials immediately after completion, and suggests that the findings be spread widely to doctors in an easy-to-understand format. Similarly, the International Committee of Medical Journal Editors—a group that includes the editors of *The New England Journal of Medicine* and *The Lancet*—and the American Medical Association are considering making drug companies register clinical trials from the outset in a public database as a prerequisite for their eventual publication (see News in Brief, page 659).

But publishing negative data carries its own set of complications. Some of these dilemmas verge on the philosophical—absence of evidence does not necessarily imply evidence of absence. But other problems are more practical, as publishing negative data is not simply a matter of stating that a given clinical trial has failed before we nod and move on to the next trial. For this information to be useful, it must be vetted with the same rigor as positive results, lest we allow inaccurate negative findings to influence clinical practice. This includes passage through the filter of the peer-review process to make sure that the experimental design and statistical analysis are sound and that any revisions that might be necessary to make it hold water properly are undertaken. As any scientist or referee knows, this process can be protracted, and there does not seem to be much incentive to producing an article that proves that the outcome one was hoping to find is not there.

At the same time, it would be disingenuous of journals—particularly high profile ones—to say that they would be equally willing to publish negative and positive data from clinical trials. In other words, the inclusion of every trial in a registry as a prerequisite for publication does not imply that the results of peer-reviewed research will be equally visible. Instead, it seems more likely that trials reporting positive results will continue to appear predominantly in high-profile publications, whereas those showing negative data might fill the pages of more modest titles, with a relatively limited influence on the decision-making process of practicing clinicians.

Although pharmaceutical companies are the targets of most criticism regarding the unwillingness to publish negative results, scientists and clinicians would be the ones investing a significant fraction of their human capital to make these data available. It is therefore questionable whether there exists enough incentive for researchers to publish negative results. Funding bodies—public or private—should begin to look more favorably on scientists who make the effort to publish negative data.

Creating a database with data from every clinical trial might benefit patients, clinicians and researchers. But its implementation and subsequent curation need to be carefully planned and will require the commitment of researchers, clinicians, scientific journals, pharmaceutical companies, funding agencies and regulatory authorities. In an era in which we are already experiencing an overload of scientific data, an unstructured deluge of information that few of us have time to process should be avoided.