The sounds of silence

Negative clinical-trial results are underreported. But this may soon change.

Sometimes, no news is news. In clinical trials, where new medical treatments are tried out on human subjects, no news – an inconclusive result, indicating that the treatment is useless, or a negative one, indicating that it is harmful – can be as scientifically important as a positive result. Unfortunately, such a result is much less likely to be reported.

That is particularly true for trials sponsored by the pharmaceutical industry which, according to the American Medical Association (AMA), accounted for over 70% of the funding for such trials in America in 2002, the most recent year for which figures are available. The lack of reporting of null or negative findings is pernicious because it skews the results of so-called 'meta-analyses', which compile data from previous studies of a treatment. If only positive results are reported, then a meta-analysis risks being too laudatory.

The medical profession has been aware of this problem for a long time. However, pharmaceutical companies have a vested interest in keeping negative results quiet, so change has been slow in coming. But the proper balance between commercial confidentiality and public disclosure in the case of drugs, where ignorance can cost lives through misprescription, is different from that for, say, computer chips. The widespread government funding of basic drug research also gives the public a moral claim on the results. And a confluence of forces in the past few weeks may well succeed in pushing drug companies towards greater openness.

The times they are a changin'

The first of these forces was a legal settlement last month between GlaxoSmithKline (GSK), a British pharmaceutical company, and the state of New York. A lawsuit filed in June by Eliot Spitzer, New York's attorney-general, alleged that GSK had deliberately suppressed negative results from four clinical trials of Paxil, an anti-depressant. In the settlement, GSK agreed to post online summaries of all of the clinical trials it completed after December 27th 2000 (the date that Glaxo Wellcome merged with SmithKline Beecham).

The second force is that on September 9th the International Committee of Medical Journal Editors, a group consisting of the editors of the *Journal of the American Medical Association* (JAMA), the *New England Journal of Medicine* (NEJM), the *Lancet* and 11 other top-flight medical publications, put the screws on those who conduct clinical trials. They announced that from the middle of 2005 their journals would no longer publish the results of trials that had not been registered in advance in an independent database open to the scrutiny of all. The journal editors do not advocate a particular database, but they do point out that clinicaltrials.gov, which is run by America's National Institutes of Health, is the only one which satisfies their criteria at the moment.

At first glance, the posturing of a few scientific journals might look puny in the face of the might of the drug companies. But the editors' proposal actually has teeth, because even hard-nosed corporations value the legitimacy that publication in an important peer-reviewed journal has on their results. And although only 14 journals have signed up to the initiative so far, other journals carrying results of clinical trials typically take their lead from the journals that are spearheading it.

Defenders of the pharmaceutical industry claim that forcing the complete reporting of results might reduce the incentive to develop new drugs by revealing a firm's hand too early in the development process. But Jeffrey Drazen, the editor of the NEJM, argues that the rewards of success are so big that requiring such reporting will not stop companies from proposing trials they think have a chance of success. What it might reduce, he says, is the number of 'seeding trials'. These are trials of drugs that have already been approved for one use, and are

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Lack of reporting of null or negative findings distorts the results of meta-analyses

then tested for secondary treatments which have little hope of success. Firms use these trials as marketing tools, to put drugs into the hands of doctors in the hope that those doctors will prescribe them more often. The mere existence of seeding trials indicates that the balance between confidentiality and disclosure is skewed.

The editors' initiative will help, but it will serve only to flush out now-hidden trials so that questions can be asked about what happened to them if no public report of their results ensues. It will not force those questions to be answered. The third factor, a political one, may deal with that.

Legislation is in the works in both houses of America's Congress to reform the reporting of trials. In particular, Chris Dodd, Tim Johnson and Edward Kennedy, three Democratic senators, are expected to propose, within the next week or two,* a law that would increase compliance with existing requirements to post trial data to clinicaltrials.gov. It would probably adopt a proposal made by the AMA that registration in a central database be a requirement for the approval of human trials, as well as introducing new requirements to include trial results in the database.

The industry disputes the need for this. Caroline Loew, a spokesman for Pharmaceutical Research and Manufacturers of America (PhRMA), a trade group, claims that the industry has a "very good history of

*The bill was introduced on October 7th 2004, and was referred to the House Committee on Energy and Commerce

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The balance between confidentiality and disclosure is skewed

compliance". This is stretching the truth. As Catherine De Angelis, the editor of JAMA, points out, a group of big drug companies agreed in 1997 that they would create a centralised database. But, because there was no enforcement mechanism, they conveniently forgot about it. Furthermore, in a letter written to PhRMA in June, Henry Waxman, a Democratic congressman from California, pointed out that the industry was not even complying with existing legal requirements to post certain trials to clinicaltrials.gov. Alan Goldhammer, another spokesman for PhRMA, claims that Mr Waxman was relying on preliminary data.

Band on the run

In his letter, Mr Waxman also complains that despite PhRMA's budget of over $72.7m for lobbying the federal government, when the House of Representatives' Government Reform Committee held hearings on the issue of clinical trials and requested that an industry spokesman testify, none deigned to show up. So there are reasons to suspect that the proposal made by PhRMA on September 7th, for a new, voluntary database, is less good than it sounds. Critics point out that it will only contain summaries of the results of trials after they are completed, rather than reporting ongoing trials. It will also be restricted to trials for drugs that are being marketed in America.

Dr Goldhammer replies that this is because PhRMA has made a deliberate decision to focus on practising American physicians, who need to know only the final results for drugs sold in America, rather than on the needs of researchers. But this is shortsighted. Researchers could make good use of the more complete set of data.

Dr Goldhammer says that what his group is proposing is "delinking a registry from a results database". That sort of obfuscation seems opposed to transparency. But transparent reporting of trials looks as if it is on its way, regardless.

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