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C. DARKIN

STACKING THE DECK

Studies of medical literature are confirming what many suspected — reporters of clinical trials do not always play straight. Jim Giles talks to those pushing for a fairer deal.

They answer only the questions they want to answer. They ignore evidence that does not fit with their story. They set up and knock down straw men. Levelled at politicians, such accusations would come as no surprise. But what if the target were the researchers who test drugs? And what if the allegations came not from the tabloid press, but from studies published in prestigious medical journals?

The slurs may sound over the top, but each is based on hard data. Since 1990, a group of researchers has met every four years to lay bare the biases that permeate clinical research. The results make for uncomfortable reading. Although outright deception is rare, there is now ample evidence to show that our view of drugs' effectiveness is being subtly distorted. And the motivation, say the researchers, is financial gain and personal ambition.

"Patients volunteer for trials, but finances and career motives decide what gets published," says Peter Gøtzsche, an expert in clinical trials and director of the Nordic Cochrane Centre in Copenhagen. "This is ethically indefensible. Change is not easy, but we must get there."

It is a dramatic conclusion to come from a field of study with no proper name, staffed by part-time volunteers. Most are journal editors, medical statisticians or public-health experts, united by fears for the integrity of clinical trials. For the devotees of 'journalology' or 'research into research', the literature on clinical trials is their raw data and patterns of bias are their results.

Some of these researchers are using their findings to change medical journals and make it harder for authors to misrepresent results. Others are working on what could become the biggest reform of clinical-trial reporting for decades: the creation of a comprehensive international registry of all clinical trials. It is a powerful idea, which could one day make all trial information public. It is also an idea that has pitched pharmaceutical companies against advocates for reform, in a tussle over whether transparency or commercial confidentiality best serves medical science.

Just say no

One of the biggest problems with clinical-trial reporting, the suppression of negative results, shows the importance of such debates. Because clinical researchers are not obliged to publish their findings, ambiguous or negative results can languish in filing cabinets, resulting in what Christine Laine, an editor at the *Annals of Internal Medicine* in Philadelphia, Pennsylvania, calls "phantom papers". If that happens, the journal record will give an over-optimistic impression of the treatments studied, with consequences for peer reviewers, government regulators and patients.

One alleged example hit the headlines in 2004. At that time, the antidepressant Paxil (paroxetine), made by London-based drug giant GlaxoSmithKline, was a popular treatment for adolescents in the United States. But doctors have now been warned off prescribing Paxil to youngsters, after evidence emerged that it increases the risk of suicidal behaviour. It was claimed in a court case brought in the United States that GlaxoSmithKline had suppressed data showing this since 1998. Rick Koenig, a spokesman for GlaxoSmithKline, says the company thought the charges unfounded, but agreed to pay $2.5 million to avoid the costs and time of litigation.

Phantom papers can be tracked down through trial protocols — the document describing how a trial will be run and what outcomes will be measured — which have to be registered with local ethics committees. By matching papers with protocols, several groups

have shown that many trials are completed but not published. And that, notes Laine, makes it impossible for journals and health agencies to assess potential drugs. "You never quite know if other data are out there that would influence your conclusions," she says.

Last year, for example, a French team showed that only 40% of trials registered with its country's ethics committees in 1984 had been published by 2002, despite more than twice as many having been completed[1]. Crucially, papers with inconclusive results not only took longer to publish (see graph), they were less likely to see the light of day at all. Researchers in any field can sit on negative or inconclusive results. But critics say that clinical researchers carry a greater ethical burden, as their findings inform decisions about the licensing of drugs.

Don't believe the hype

Nor do the problems end when a trial hits an editor's desk. Results from a trial of the arthritis drug Celebrex (celecoxib) looked good when they were published in 2000, for example, but less so when physicians scrutinized the full data set. The original paper, which appeared in the *Journal of the American Medical Association* (*JAMA*), dismissed fears that Celebrex could cause ulcers. But that was based on data collected over six months. When other physicians analysed a full year's worth — which the authors already had at the time of their *JAMA* submission — they claimed that Celebrex seemed to cause ulcers just as often as other treatments[2]. The original study's authors say that the later data were too unreliable to be included, but acknowledge that they could have "avoided confusion" by explaining to editors why they had omitted them.

This case is not a one-off. During his PhD at the University of Oxford, UK, epidemiologist An-Wen Chan looked at the protocols for 122 trials registered with two Danish ethics committees in 1994–95. More than half of the outcomes that the protocol said would be measured were missing from the published paper, he found[3]. Asked about the missing outcomes, most authors simply denied the data were ever recorded, despite evidence to the contrary. And when Chan looked at those missing data, he found that inconclusive results were significantly more likely to have been left out of the final publication.

J. RAEDLE/GETTY IMAGES

Bitter pill? GlaxoSmithKline denies suppressing data about antidepressant Paxil's side effects.

Medical journals can, however, request such missing data. One idea, adopted by *The Lancet* three years ago, is to insist that authors send in a trial protocol when they submit results. That should help identify whether researchers are reporting all the information they gathered.

But even with all the data, journal editors face another challenge: hype. Researchers and sponsors tend to be interested in things that work rather than those that do not, so authors may subconsciously tweak results and talk up conclusions. "Researchers are so worried about getting papers rejected that they put a lot of spin on results to make them seem as exciting as possible," says Doug Altman, a medical statistician who supervised Chan at Oxford.

The hype shows up in a paper's conclusions. In 2003, epidemiologist Bodil Als-Nielsen and her colleagues at the University of Copenhagen looked at factors that might influence researchers' conclusions about a drug's efficacy or safety[4]. Their analysis of 370 trials showed that the strongest predictor of the authors' conclusions was not the nature of the data, but the type of sponsor.

Trials funded by for-profit organizations were significantly more likely to reach a favourable verdict than those sponsored by charities or governments. Critically, the association was not explained by the papers having more positive results. In a study under review, Gøtzsche and his colleagues show that industry-funded meta-analyses — studies that combine results from several clinical trials of a drug — are similarly prone to draw positive conclusions that are not supported by the data (see graph).

For many clinical-trials experts, these funding biases explain all the others. For each act, be it the suppression of results or the omission of outcomes, there is a financial motive for the company whose drug is being tested. In many cases, the company funding the study also employs one or more of the authors. Given the combination of motive and opportunity, many see drug-company influence as an inevitably distorting factor.

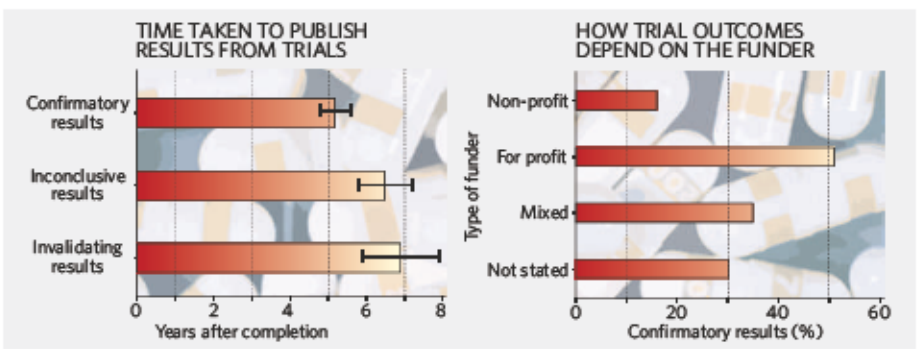
"When we see an industry article we get our antennae up," says Steven Goodman, a medical statistician at Johns Hopkins University in Baltimore and an editor at the *Annals of Internal Medicine*. "It's not that we assume the research is done badly. But we have to assume that the company has done all it can to make its product look as good as possible."

Editorial control

At *JAMA*, editors began insisting last year that all research sponsored by for-profit organizations undergo independent statistical analysis before acceptance. Cathy DeAngelis, the journal's editor-in-chief, says *JAMA* had asked authors to do this for years, but began requiring it after editors started seeing papers that they thought dishonest. "People said that for-profit companies would stop sending us trials," she notes. "Well, guess what? If you look at what we're publishing you'll see that that's not true."

Still, Goodman and others caution against blaming everything on industry. Government-sponsored trials also tend to report positive outcomes[5], although the effect is weaker than with industry studies. And a publication in a big journal can boost authors' careers as well as company coffers.

Others add that journals must also share the blame. Good peer reviewers and hands-on editors should, for example, weed out hype. But according to Richard Smith, a former editor of the *BMJ* (which was the *British Medical*



SOURCES: REF. 1; REF. 4

JACOB RIES

"Patients volunteer for trials, but finances and career motives decide what gets published." — Peter Gøtzsche

Journal) and now head of European operations for the US insurer UnitedHealthcare, editors may be biased towards positive results. In an article published last May, titled "Medical journals are an extension of the marketing arm of pharmaceutical companies", he pointed out that reprints of papers reporting positive results can generate millions of dollars, and that this might influence editorial decisions[6].

There is certainly evidence that drug companies attempt to use reprint income as a lever on journals. *The Lancet*'s Richard Horton has said that authors sometimes contact him to say that sponsors are likely to buy large numbers of reprints if their study is published. Horton and other editors at top journals say they rebuff such threats, but some less well staffed journals lack policies for separating commercial and editorial decisions, suggesting that reprint income at least has the potential to distort decisions.

Merrill Goozner, who tracks pharmaceutical issues at the Center for Science in the Public Interest, a lobby group in Washington DC, agrees. "It's a financial conflict of interest, plain and simple," he says.

Full disclosure

Such accusations make medical editors angry. They deny that commercial pressures influence peer review, adding that journals have introduced several measures that have helped to clean up clinical-trial reporting.

One of the first initiatives, introduced in 1996 and revised in 2001, is the statement on Consolidated Standards of Reporting Trials (CONSORT). A set of guidelines on how to report a clinical trial, the statement is designed to ensure that authors present results transparently. It seems to be helping. Since top journals began insisting that authors follow the guidelines, researchers' descriptions of their methods, for example how they place subjects in treatment or control groups, have become more accurate[7]. Such information aids reviewers' decisions.

Journals have also endorsed trial registries. By registering all trials when they begin, researchers will find it harder to suppress outcomes, editors believe. Several registries already exist, including one run by the US government. The World Health Organization (WHO) is working on an online portal that would bind these databases into a single source. And in 2004, the International Committee of Medical Journal Editors announced its members would not publish the results of trials that had not been placed in a public registry.

Clinical-trials experts welcomed the move, but the industry response was patchy. Last June, the committee was forced to issue another statement after finding that some sponsors were being deliberately vague and entering terms such as 'investigational drug' in the field for the drug name. A follow-up study found the quality of information had improved considerably by last October[8].

Despite these successes, advocates of reform say bigger fights lie ahead. The experts working on the WHO registry want a list of mandatory entries for trial data, including the primary outcome. For drug companies this is a step too far, akin to asking an inventor to publish the description of an invention before it is patented. Instead, the companies propose depositing such information in a locked database, to be released when the drug obtains marketing approval. Going public too early,

IMAGE UNAVAILABLE FOR COPYRIGHT REASONS

On the record: journals have begun demanding more transparent registries of clinical trials.

S. GOODMAN

"We have to assume that the company has done all it can to make its product look as good as possible." — Steven Goodman

they say, would deter companies from taking risks on potential treatments and slow down the generation of new drugs.

Yet for critics such as Smith, even the WHO portal does not go far enough. Along with other registry advocates, he would like to see all clinical results, not just protocols and outcomes, published in public databases.

This proposal would seem to tackle problems with reporting data and bias. But it would not be simple. Aside from the commercial concerns of the drugs industry, the creation of a results database could lead to patients pressurizing doctors for access to experimental medicines. Health insurers and hospitals might also change the drugs they use after seeing the raw results, rather than waiting for peer-reviewed papers.

The debate is in its infancy. Yet clinical-trials experts are more optimistic than they have been at many points in the past 15 years. Chan, now working for the WHO registry team in Geneva, says the first round of consultations with stakeholders should produce a policy statement in April. He and others add that although industry will probably continue to resist, the public attention generated by recent scandals, and the wealth of data available on the problems, mean that time is ripe for change.

"I'm not relying on hope," says Gøtzsche. "But the results of all trials should be made public, not only those that the sponsor cares to tell the world about. This is incredibly important." ■

R. FARIS/CORBIS

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