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The "file drawer" phenomenon: suppressing clinical evidence

Accumulating evidence, including a report in this issue by Bhandari and colleagues, (see page 477) suggests that commercially sponsored clinical trials are biased toward obtaining positive results. Laurence Hirsch, vice-president of medical communications at Merck, argues in an accompanying commentary (see page 481) that while drug companies are likely to give "priority" to trials with the greatest likelihood of "positive return," the sources of bias in clinical trials of any funding stripe are difficult to tease out. But, clearly, a substantial proportion of clinical trial results is simply never reported in the public domain. Most go unreported because a treatment effect was not shown — the so-called "negative" study. But, in other cases, trial results are a commercial liability. The huge investment required to develop new drugs and devices and successfully carve out a share of the market for them puts pressure on companies to suppress results that might slow or extinguish sales. No surprise that selected clinical trial data are kept locked in the filing cabinet.

By concealing unfavourable evidence about efficacy and safety, pharmaceutical companies deceive physicians, their patients and, perhaps, shareholders. Worse, such concealment is a flagrant abuse of the trust freely offered to study investigators by research subjects. Nowhere is this more evident than in clinical trials of selective serotonin reuptake inhibitors (SSRIs) in children. Although depression is not an easy diagnosis to make in the often turbulent emotional life of children and adolescents, by age 18 about 20% of adolescents will have experienced an episode of major depressive disorder, lasting some months, and carrying the threat of recurrence. This large market of child and parent anguish has attracted pharmaceutical companies.

Jane Garland, a psychiatrist and clinical researcher, has been an investigator in a few trials of SSRIs in children (see page 489), not all of which have been published. To review product information before participating in one industry-sponsored trial she was obliged to sign a 10-year nondisclosure agreement. This embargoed information included a summary of negative data from previous unpublished trials that showed a lack of effectiveness for a drug already on the market. Garland has voiced to us and to others her resolve to "never do an industry-funded trial again unless the whole structure and management of these is drastically changed." She laments the fact that physician–researchers have not taken a collective stand on the disclosure of trial data.

Concealment occurs also at the level of government regulation. Given that companies seeking drug approval must report all trials to regulators, Health Canada cannot be oblivious to buried trials and conflicting evidence of efficacy and safety. Yet, constrained by laws with conflicting goals — to provide the public with safe and efficacious drugs and devices *and* to protect commercial interests — regulators are too often silent.

Other hidden evidence in the hands of regulators takes the form of adverse drug reaction reports. Andrew Herxheimer and Barbara Mintzes (see page 487) comment that, even in the United Kingdom, which has one of the best voluntary reporting systems in the world, the side-effects of drugs used to treat depression are underreported and hence underestimated.

The behaviour of industry, government and investigators must change. Investigators must demand access to all the data collected in clinical trials in which they participate[1] and to suitably anonymized aggregate information from adverse drug reaction reports. Investigators should be at liberty and even encouraged to provide alternate analyses and interpretations of clinical trial results and adverse event reporting and to publish these. Physicians, research subjects and the public should demand no less.

We are encouraged by Hirsch's announcement that "Merck has adopted guidelines in which we commit to publish the results of hypothesis-testing clinical trials regardless of outcome." Although some may find fault in the details, the new Merck guidelines are a bold step — one that should receive wide support and encouragement from the research community and physicians. Canada's Research-Based Pharmaceutical Companies should announce their full support for the Merck guidelines and make them part of the association's guidelines for all member companies.

We hope that with the proposed "renewal" of Canadian health protection legislation, our government will adhere to the stated values of "openness," "accountability" and the "primacy of health and safety."[2] In the regulation of clinical testing of drugs and devices, safety and efficacy must trump proprietary rights every time. — *CMAJ*

References

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2. Health protection legislative renewal [proposal]. Ottawa: Health Canada; 2003. Available: www2.itssti.hc-sc.gc.ca/HPCB/Policy/LegislativeRenewal.nsf (accessed 2004 Jan 26).