



Conflict of interest crisis

Researchers and regulators at odds over reform proposals

On 7 December, 2003, the two-time Pulitzer Prize winning journalist David Willman published a devastating indictment of the US National Institutes of Health in the Los Angeles Times. His findings are especially relevant at a time when the EU is considering the best way to establish a pan-European medical research framework.

Five years in the making, Willman had trawled through thousands of emails, financial disclosure reports, memos, company reports, legal actions, patent applications and regulatory filings. His 12,000-word piece documented how hundreds of highly paid NIH scientists had earned a total of millions of dollars in fees and stock options from pharmaceutical and biotechnology companies. One researcher had made more than \$1.4 million in consulting fees, plus stock options, over a decade.

The story generated seismic ructions, and the implications are still unfolding, not just for the NIH but for relations of clinicians and academics with the industry in general – in both the US and Europe.

The LA Times story prompted investigations from the House of Representatives Energy and Commerce Committee, and the Senate Appropriations Committee. Having doubled the NIH budget over the previous decade, to nearly \$28 billion per annum, they had a vested interest in how it was being spent.

As Robert Steinbrook put it, in a New England Journal of Medicine editorial in January 2005, "Collaborations can raise questions about whether researchers are placing a higher priority on the needs of their industry collaborators or their personal financial well-being than on the safety of research subjects and the integrity and openness of the research environment."

Sweeping reforms proposed

The outcome was that Dr Elias Zerhouni, Director of the NIH, announced sweeping ethics reforms in February this year. Senior scientists (about 6,000 people) would be prohibited from entering into outside consulting agreements with pharmaceutical companies, hospitals, health insurers and healthcare providers. The new rules further mandated that they and their families must divest of all stock in pharmaceutical and biotechnology companies. The guidelines also banned scientists from accepting even uncompensated professorships and board positions with professional societies on their own time, or any remunerated prizes

except for the Nobel Prize. The new rules are similar to those governing employees of the FDA, although Zerhouni noted, "NIH is not a regulatory body, but a scientific organisation, and the rules could restrict important scientific interactions".

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Dr Elias Zerhouni

NIH researchers did not take the new guidelines gladly. At a meeting on February 2nd, the day before the regulations went into force, hundreds of employees vented their rage at Zerhouni's "drastic restrictions". The Washington Post reported the events at the meeting as "Restrictions on Outside Income Meet with Derision at Meeting". The Assembly of Scientists, an elected body of 15 NIH researchers who represent employees throughout the agency, later distributed a newsletter in which they claimed that the ethics guidelines "Substantially overreach and will severely and irreparably compromise the NIH's mission" because they "discourage talented, innovative scientists from staying at, or being recruited to the NIH, and preclude current NIH scientists from participating as full members of the scientific community."

Zerhouni explained he had tried to "stand up for his troops" but had been "shot in the back" with the discovery, made by congressional investigators, that more than 100 NIH employees had not disclosed various relationships with pharmaceutical companies. The congressional investigators had approached 20 pharmaceutical and biotechnology companies directly, to obtain a list of NIH consultants. Zerhouni described this as a 'tipping point', saying, "I have reached the regrettable conclusion that some NIH employees may have violated the existing rules and that the agency's ethics system does not adequately guard against these violations."

However, an internal NIH review later showed that as many as 80% of 'consultants' had been wrongly named: they had apparently received NIH approval for consulting work, or there had been a clerical error in reporting their names (either a mix-up over the year in question,

or a confusion over two people with the same name). Given that Zerhouni had described these violations as the tipping point, some NIH researchers argued that the new guidelines should be redressed accordingly. To a point they are being redressed; temporary Fellows, for example, are now to be exempt from the new rules.

Meanwhile, the Assembly of Scientists is pursuing other legal strategies to challenge the new rules. They hired the legal firm Arent Fox to represent their interests on Capitol Hill. David Willman, author of the original LA Times report, was quick to rake muck, in a news piece for the LA Times on April 21. Referring to the Assembly of Scientists as 'a group of dissident agency scientists', his opening sentence said it all: "Scientists at the NIH who are fighting new rules that would end their financial ties to the drug industry have hired, at a favourable rate, a law and lobbying firm that also represents the companies." Arent Fox denies receiving industry funding to subsidise the NIH scientists.

Later in his piece, Willman takes Rick Weiss of the Washington Post to task for his favourable coverage of the NIH scientists' position. Citing two supportive editorials, along with several news articles, Willman says the "dissident NIH scientists have sought through news articles and opinion columns to cast the new rules as damaging to the agency."

What, we might well ask, does all this mean for ophthalmologists? For one thing, the NIH includes the National Eye Institute, which supports eye research around the world and has undertaken some of the largest, most important studies in the field, including AREDS (Age Related Eye Disease Study) and OHTS (Ocular Hypertension Study).

Root of the Problem

The troubles at the NIH date back to the mid 1990s, when Nobel laureate Harold Varmus was Director. Varmus was faced with a problem. Most of the agency's budget does not go to the 17,000 direct employees of the NIH, known as 'intramural' researchers, but to the extramural programme, which funds scientists working in universities and hospitals all over the US and beyond. These scientists are not subject to the same ethical guidelines that govern federal scientists. But a gap was opening in standards. Varmus had to respond to criticisms that the science in the intramural programme had become inferior to that in the extramural programme.

Seeking to revitalise the NIH intramural programme, by recruiting and retaining top scientists, Varmus relaxed the ethical guidelines, which at the time were stringent, prohibiting federal scientists from consulting

or lecturing for outside organisations that had business dealings with their laboratory or branch. They were also prohibited from accepting stock options as payment for outside activities, and their total outside payments were capped at \$50,000 per year (and \$25,000 from a single source). In relaxing these guidelines, and helping convince Congress to double the NIH budget, Varmus is credited with improving the NIH scientific programme.

But how is the quality of a scientific programme judged? This question is at the root of the NIH conflict-of-interest scandal, and applies equally to European programmes of clinical research. The problem is that research groups are judged at least in part by their success at technology transfer – the commercialisation of academic research findings.

From the point of view of taxpayers it is reasonable that governments should support research that has potential for a return on investment. But in encouraging applied science, governments encourage commercialisation. The cost of taking a candidate drug to the market is astronomical, and not within the remit of government or academic research. The NIH, for example, cannot legally produce or market drugs. On the other hand, pharma companies are unwilling to pay for all basic research, most of which comes to nothing, so there is the grey area of technology transfer, where it is not clear who 'ought' to fund commercialisation. At present, technology transfer is funded by venture capital, and it is the practical realities of this system that underpin the conflicts of interest.

Few would dispute the need to commercialise scientific knowledge gained in the federal labs, but the manner in which agreements were signed does raise some questions. The cancer drug paclitaxel (Taxol) for example, was developed over 30 years at NIH, at a total cost to the taxpayer of about \$484 million. Eventually NIH entered a transfer agreement with Bristol Myers Squibb in 1991. Under the deal, BMS took all the NIH research, completed the clinical trials, and marketed and priced the drug autonomously, a total investment of about \$1 billion. The NIH received a 0.5% cut of sales as royalties. Taxol went on to be the highest selling cancer drug in history, earning BMS some \$9 billion, a 900% return. The NIH, in contrast, made just \$35 million in royalties, recouping but 7% of its investment. To add insult to injury, Medicare paid \$687 million for Taxol between 1994 and 1999, at a charge per dose roughly \$500 more than private doctors.

All this was revealed in a government report from June 2003, six months before the LA Times story broke. The problem,

according to Keith Ashdown, VP of the non-partisan Taxpayers for Common Sense, was that the negotiations had "failed largely because NIH is overwhelmingly concerned with esoteric research to the detriment of concern for the bottom line."

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Of course there had been no guarantee that Taxol would be a runaway success – the NIH had not completed a clinical trials programme, and BMS were taking a gamble that happened to pay handsomely. But after such failures, the NIH and the university sector in general were under pressure to be more commercially astute about technology transfer. The commercial reality is that the majority of products in the clinical trials pipeline fail to reach market. To progress a patented candidate drug with clinical potential to a clinical trial requires venture capital, and venture capitalists aim for a swift return on their investment. To successfully attract venture capital, academic researchers must become commercially involved in a competitive hard sell to industry.

The commercial reality

One academic ophthalmologist involved in a start-up biotech, who did not wish to be named, told EuroTimes, "There are very strong commercial pressures on a start-up biotech company. There are good guidelines from organisations like the Wellcome Foundation, but they're not realistic in terms of the practical demands. They attempt to limit the commercial involvement of researchers, but unless a researcher is willing to take a big equity commitment to show belief in the product, there's no way you're going to attract capital. The people who put up money are middle-aged guys in grey suits that know nothing about medical research. They don't need to, they're judging the people, and if you want to attract venture capital they need to believe that you can return their investment."

It's perhaps worth recording that the Wellcome Foundation supplied me with their guidelines, which do state that it is "desirable to encourage, where appropriate, scientifically productive relationships between Trust-funded researchers and commercial organisations" but Wellcome would not put anyone forward for interview by EuroTimes, saying, after a little pressing, "we don't wish to add anything to the information already sent" (the guidelines, available at <http://www.wellcome.ac.uk/assets/wtd005845.doc>).

The long and short of it is that both government and charitable funding agencies, in the US and Europe, have for nearly two decades encouraged commercialisation of clinical research for the benefit of the taxpayer. The most successful universities at technology transfer are the most commercial in attitude. A shift in tone began in the late 1990s, when universities became more sophisticated in their attitudes to technology transfer. Greg Gardiner, for example, who had spent 22 years running Pfizer's external biotechnology investment strategy, became the Director of Yale's Office of Cooperative Research in 1996, and his aggressively commercial strategies revolutionised technology transfer, not just at Yale, but all across the US academic world. One bruised venture capitalist said, "I've never encountered people like Greg Gardiner in a university environment before."

In this respect, the NIH is no different. It has about 275 cooperative research and development agreements with industry, and 1500 active licenses, as well as patents and patent applications. If the intramural programme is to maintain comparable standards to the extramural programme, and the US taxpayer is to reap any value for money, then NIH researchers must be commercially involved. In the climate of the times it is no longer feasible for researchers to be dispassionate seekers of truth, for they must be committed advocates of their own research, and its value for the public good. If this situation is commercially tainted, what might be done?

The Long Reach of Industry

The NIH is only part of the story. Conflict-of-interest has become a watchword of our times, and there is no doubt that journals have woken up to the problem over the last decade. Long lists of financial disclosures are declared with every other article. Most clinicians are involved in clinical trials, and so work directly with industry, rather than courting venture capital.

But conflicts of interest are just as real, and not just financial. Douglas Koch, MD, Co-Editor of the Journal of Cataract and Refractive Surgery, listed 14 types of conflict in an influential 2002 editorial, ranging from the kudos of being a 'pioneer' with early access to new technology, to sponsorship of meetings, academic advancement, inclusion on clinical publications written under the auspices of the manufacturer – "and, yes, ego gratification."

As Ian Schorr MD, an ophthalmologist with an interest in regulatory issues, has pointed out, even recommending (selling) surgery is a potential conflict of interest – "of course it is, and that is why the mandated second opinion came about."

Publications are perhaps the most insidious form of deceit, for many are ghost-written by medical writing agencies on behalf of pharmaceutical companies, though this is only rarely acknowledged in the journals themselves. Even so, it is easy to see how the present situation developed.

Paul Rosen, FRCS Medical Editor of EuroTimes, said "For a clinical trials unit in a

hospital or university, it is considered a coup to keep the publication rights, allowing you to publish what you want."

It's easy, though, to imagine a busy academic postponing the burden of writing up important results, perhaps even for years. For a pharmaceutical company, time is money. What if they were to prepare a first draft, just to speed the process along? In time, a first draft turns into all the drafts of an exhaustive publications plan, submitted to the journals directly by the agency involved, but never featuring their name: a deceit, if an understandable one. And the academic ends with an extensive publication list, an international reputation, and promotion to head of department.

According to Rosen, "The answer to good industry relations is transparency. Industry funding is necessary for clinical research, and immensely valuable for the education of physicians. They are significant sponsors of most of our large meetings, as well as our journals through advertising. They are our partners, but we need to know if research is directly sponsored by industry. If the presentation or paper comes from an industry sponsored project you don't necessarily disbelieve the results, but you are likely to scrutinise them more."

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Warren Hill MD, Chair of the ASCRS CME advisory committee, agrees. "The assumption is that anyone with any type of relationship with a commercial interest is immediately corrupted by that relationship. That assumption is wrong. The proper way to deal with conflict of interest is to disclose financial relationships so that all who have access to information can evaluate it in light of that disclosure. Medical science flourishes in an environment of robust debate and the free flow of ideas and information."

Despite his sweeping ethics reforms at the NIH, Zerhouni, too, is pragmatic. "Transparency – full light on any relationship – is one of the best protections against any real or perceived conflict of interest.... What is being portrayed in the press about the NIH is not the reality, but that doesn't mean we couldn't do a better job of managing the conflict issues."

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