
GRETCHEN MILLER

US clinical-research system in need of review

An imminent rethink is required on the country's approach to government-supported health and pharmaceutical studies, says **Arthur J. Ammann**.

It is time for a far-reaching and comprehensive review of the way US government-backed clinical research is funded and approved. Ethical reviews of much of this work are currently inadequate and problems come to light too late.

In the most recent example, the US Department of Health and Human Services (HHS) judged that researchers carrying out a study on optimal oxygen administration in infants of low birth weight had failed to fully inform parents about the risks involved.

Clinical researchers defend such studies. But it is clear that too many institutional review boards (IRBs), which give clinical studies the green light, do not have the expertise to thoroughly review the science and ethics of complex clinical trials.

Ethical abuse was certainly more common in the past, and modern science likes to think that it has cleaned up its act. There was an outcry after it was revealed that the US Public Health Service deliberately exposed mentally incapacitated patients, prisoners, sex workers and soldiers to syphilis and gonorrhoea in Guatemala in the 1940s. Officials, including Francis Collins, director of the US National Institutes of Health (NIH) in Bethesda, Maryland, insisted that such unethical studies would be impossible today. Yet a report from the Presidential Commission for the Study of Bioethical Issues in Washington DC challenged that denial. The commission concluded that it "cannot say that all federally funded research provides optimal protections against avoidable harms and unethical treatment".

On closer examination, the promised impervious wall of ethical protection is riddled with cracks. Progress in clinical research, complicated by the reach of science across borders, has outpaced the ability of researchers and IRBs to make fully informed decisions. The problems are detailed below.

There is inadequate expertise: the composition of IRBs has not kept pace with the complexities of ethics and science. Expert opinions are often derived from individuals who lack sufficient expertise to make an informed decision.

There can be conflicts of interest: individual IRB members may gain salary, health and retirement benefits from approval of research studies conducted at their institutions, which may also make gains.

Exclusivity issues: the design and ethical review of federally funded research is often undertaken by a homogeneous group of individuals with congruent interests at the same or similar academic institutions. Individuals from the public, advocacy groups and non-academic organizations are often excluded. When people from these groups publicly voice their concerns, their views are vilified in academic publications as impeding future advances in research, or even ignored.

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Marked increases in funding: the NIH budget for research in 2011 was more than US$30 billion. Large amounts of money can distort priorities for research and shift the focus away from urgent public-health needs on the basis of the belief that all research products merit clinical evaluation. The number of products in the therapeutic pipeline is rising and there is no informed method for prioritizing those which should move into clinical research. This increases the risk for people who participate in research.

Increased cost of clinical research and fewer treatment-naive individuals (those who have not been treated with any drugs of the class in question) in the United States: the number of research participants required to obtain statistically significant results for new products has increased drastically because of the need to compare these products with ones that are known to work. A 'mining' approach to obtaining treatment-naive people for research in poor countries has evolved, enlisting vulnerable populations. In some circumstances, the stated benefit for the individual may be limited to the future good of 'mankind', a concept not easily understood in cultures in which health care is deficient. The shift to resource-poor countries is often accomplished by reducing standard of care, exaggerating potential benefits, the use of inferior treatment comparisons and the enrolment of vulnerable people not fully informed of their legal or ethical rights. Although the use of such practices has previously seen pharmaceutical companies criticized, they are increasingly used in academic circles to justify clinical trials funded by the federal government.

A common defence is that breaches of ethical and scientific guidelines are rare. But the Presidential Commission's conclusion clearly states that there is a problem. And the World Medical Association has recently called for revisions of its ethical guidelines, emphasizing that concerns are widespread.

These issues must be resolved before the cracks become fissures. The HHS, the NIH and universities must acknowledge that the current research-approval process is flawed and requires an urgent, comprehensive review that should include experts and leaders from outside the academic community. This review must assess and make recommendations on how research priorities can be established, the means to select the most deserving products for clinical trials, how to expand IRB membership to include greater scientific and ethical expertise, how to minimize conflicts of interest and how to increase public input into decision-making for clinical research. ■

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