US exceptionalism comes to research ethics

Comment by Peter Lurie in The Lancet (HRG Publication #1732)


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"The survival of liberty in our land increasingly depends on the success of liberty in other lands. The best hope for peace in our world is the expansion of freedom in all the world"
US President George W Bush, Inaugural Address, Jan 20, 2005

A defining characteristic of US President George Bush's recent inaugural speech was his universalist call to facilitate the global spread of liberty and freedom. Seeking an expansive vision for his second term, the President declared that "There is only one force of history that can break the reign of hatred and resentment, and expose the pretensions of tyrants, and reward the hopes of the decent and tolerant, and that is the force of human freedom".

There is thus no small irony in recent US actions which have placed that nation at odds with prevailing opinions and standards in the international community. For matters that affect public health, in the past decade or so, the USA has either withdrawn from or failed to endorse the Kyoto Treaty on climate change, the Treaty on the Limitation of Anti-Ballistic Missile Systems, the Biological Weapons Convention, the Comprehensive Test Ban Treaty, and the (Land) Mine Ban Treaty.

It should not be surprising, therefore, that this flair for exceptionalism has also infected US policies on human experimentation. In June, 2004, the US Food and Drug Administration (FDA) proposed that clinical research projects abroad that are not conducted under an application for an investigational new drug (IND) need no longer comply with the Declaration of Helsinki, a document described by the Canadian Medical Association as "the stone tablet of medical research ethics".

At issue are certain studies outside the USA without an IND application that might not come to the attention of the FDA until a drug company later seeks approval in the USA by filing a new drug application (NDA). Current FDA regulations require studies submitted in support of such an NDA to have been done in a manner consistent either with the Declaration of Helsinki or any local laws, whichever is more protective for patients. The FDA's proposal would remove these requirements entirely and mandate only that the submitted studies be consistent with the Good Clinical Practices (GCP) guidelines of the International Conference on Harmonisation. However, the GCP guidelines were not developed transparently and mainly address procedural issues, not overarching ethical ones. The GCP guidelines do not, for example, address conflict of interest, the need to publish results, or post-trial availability of successful treatments to study participants or community members, topics included in the Declaration of Helsinki. The agency states that it is concerned with "ensuring quality of data" and that the GCP guidelines are therefore necessary. Why not simply have FDA regulations refer to both the GCP guidelines and the complementary Declaration of Helsinki?

The FDA also worries that the Declaration of Helsinki could be modified "independent of FDA authority", although the GCP guidelines themselves are not immutable, and the agency does acknowledge that any revisions "could not supersede US laws and regulations". Ironically, the FDA has already deftly evaded the 2000 modifications to the Declaration of Helsinki by declaring in 2001 that the reference to the declaration in FDA regulations was not actually to the current version, but rather to the weaker, now defunct 1989 version.

The FDA and other agencies within its parent agency, the Department of Health and Human Services, and the US drug industry have led the charge against many
substantive improvements in several international ethics documents. Their efforts have been least successful with the Declaration of Helsinki, providing an alternative motivation for the FDA's proposal. In reports dating back to 1996,8-12 and in meetings about the Declaration of Helsinki and a related document prepared by the Council for International Organizations of Medical Sciences, the Department of Health and Human Services and its agencies have spearheaded efforts to limit the rights of participants in clinical trials and their communities, particularly in developing countries.

The FDA's concerns have focused on two areas, both conveniently absent from the GCP guidelines. For placebo use, the FDA complained that the language in the 2000 Declaration of Helsinki precludes the use of placebos in studies of minor conditions. By exerting influence unavailable to the less influential, the agency succeeded in forcing through a "clarification" that permits such use. And the FDA defends the use of placebos in studies of treatable life-threatening conditions in developing countries,13 and fears that the Declaration of Helsinki precludes such trials.

The Department of Health and Human Services and the FDA have also argued forcefully against the requirement in the Declaration of Helsinki that effective drugs be provided to all study participants at the conclusion of the research.11 This requirement is particularly critical in developing countries, where, due to poverty, those in the active study arm might see their drugs abruptly discontinued and those in the control group might be denied the benefits of the very therapies whose efficacy they have just helped prove. The FDA representative at the September, 2003, meeting of the World Medical Assembly failed to get this provision reversed. The same kinds of pressure were applied to the revision of the guidelines from the Council for International Organizations of Medical Sciences with more success.

The Department of Health and Human Services and its daughter agencies, ably assisted at times by the US drug industry, have crafted a strategy that has reached its apotheosis in the current FDA proposal. In a particularly Orwellian touch, the National Institutes of Health (also part of the Department of Health and Human Services) recently relied heavily on ethics documents developed in the USA and the UK, as well as the heavily US-influenced document from the Council for International Organizations of Medical Sciences, to declare that the Declaration of Helsinki does not represent the "consensus view" on the use of placebos in developing-country trials.11

The Declaration of Helsinki is not a perfect document. But at least it has the virtue of being the product of a quasi-democratic process. The declaration is produced by the World Medical Association--82 national medical associations (government agencies cannot be members). The declaration can be amended only by a formal vote before the full World Medical Assembly, which meets annually. By contrast, the guidelines from the International Committee on Harmonisation are the product of negotiations by just six parties: the regulatory authorities and drug industries of the USA, the European Union, and Japan. Input from consumers and developing countries asymptotically approaches zero.

The Declaration of Helsinki is the standard-bearer for international research ethics and enjoys particular respect in the developing world. It would be tragic if the US tendency to arrogantly flout international mores claimed the declaration as another victim, even as the President touts the universalism of human rights.

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