

Developing Responsible Policies for International Clinical Research.

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In the not too distant past, when we discussed human medical experimentation, it brought to mind the horrors of the Auschwitz concentration camp and the infamous Josef Mengele, also known as the Angel of Death. In response to this immoral testing, the Nuremberg Code was written to provide universal directives for any experiments or research including human participants. The international community took this measure to protect people from injury, disability, or even death. Paramount was the section of the Code that emphasized, among others, the necessity to obtain voluntary, informed consent from subjects.

Since that time the scientific community has taken great strides to further ensure the safety of human subjects.^{1,2,3} Unfortunately, despite the protections instated by the Nuremberg Code and other medical ethics codes, a new wave of testing scandals has emerged regarding the ethical involvement of human subjects in poor or underdeveloped nations.

The recent film based on a novel by John LeCarre, *The Constant Gardener*, is a fictional account of drug testing by pharmaceutical companies on the poor of the Third World. In this movie, pharmaceutical companies are willing to accept the deaths that may occur from illegal testing as part of a more profitable way of bringing a drug to market. But would drug companies *really* do this?

The recent verdict against the makers of Vioxx shows that a jury thought Merck sold a drug it knew was dangerous. Unfortunately, this is not an isolated concern considering these other recent events:

- A panel of Nigerian medical experts recently concluded that Pfizer Inc. violated international law when in 1996 it tested an oral form of Trovan—an unapproved drug—on children. The inquiry further demonstrated that there was no documentation that patients or their parents were informed of the testing and that the approval letter from a Nigerian ethics committee had been fabricated and backdated.⁴
- In 2003, a series of articles in the *Monthly Index of Medical Specialties* exposed the illegal trials and illegal promotion of the anti-cancer drug Letrozole in India. More than 400 Indian women were enrolled without their knowledge or permission to take part in clinical trials to see whether the cancer drug would also induce fertility. It has been reported that the pharmaceutical industry in India often has a “cozy relationship with regulators and bribe researchers, hired to conduct purportedly independent clinical trials, with expensive gifts like cars, paid speaking engagements, over-paid consultancy work and free overseas holidays.”⁵

Why have so many clinical trials gone abroad?

The incentive to take clinical trials abroad begins with the drug approval process. In the United States, in order to gain FDA approval for a new medication referred to as a “new chemical entity”, or NCE, a researcher or a pharmaceutical company must first prove that its product is safe and effective. To be approved for sale in the United States, an NCE must first be proven safe in animals and then thoroughly tested in humans over the course of three trial phases of increasing size, complexity, and duration. The purpose of these varying human studies is to determine bioavailability, dosing regimens, safety, side effect profiles, and efficacy for each new therapy. Unfortunately, as illustrated in Table 1, the rigorous process of bringing a new drug to market carries some costly pitfalls for sponsors.⁶

Table 1. Challenges to bringing an NCE to market

Phase of research / Research issue	Challenge
Animal laboratory testing	Most drugs do not survive beyond this stage
Clinical trials with human subjects	80% of NCEs that reach human testing are not approved
Human clinical trials	This facet of the NCE to market process represents 60% of R & D costs
Financial investment for introducing a new drug	The approval process generally costs \$359 million per drug
Profitability of Research and Development (R&D)	Between 1980 and 1984 only 30% of approved drugs recouped their development costs
All phases of the necessary testing to bring an NCE to market	The full approval process takes an average of 12 years

The US patent law is an additional concern in this industry.⁶ At present generic equivalents for FDA-approved drugs cannot be introduced until the original manufacturer’s patent expires. What works against pharmaceutical companies is that they must file patents on NCEs in advance of preclinical testing (i.e., animal studies) thereby leaving less time to recoup the R & D costs while the patent is in place. To alleviate these financial concerns, pharmaceutical companies have sought ways to reduce both drug development costs and approval times. While this may expedite the arrival of life-improving or life-saving drugs, and give pharmaceutical companies a better chance of recouping their enormous research expenditures, we must make sure that safety and efficacy are not compromised by this acceleration.

An increasingly popular way to reduce overall costs and expedite the testing process is by conducting clinical trials overseas and then submitting the collected data to the FDA for U.S. approval. Conducting research in poor and developing regions such as Africa, the Middle East, Central and Eastern Europe, and Central America can significantly lower costs and speed up approval

times as well as provide high patient availability, an abundance of diseased populations, lax regulations, and low investigation fees.⁶ In poorer nations, the lack of insurance, the cost of medicines (if they are available), and the excess of disease morbidity and those in need of treatment make recruitment and enrollment relatively quick and easy.

A formula for abuse

Perhaps the key ethical issue researchers must tackle regarding research in poorer nations is the issue of consent. According to codes in virtually all Western, developed countries, study participants must sign an informed consent document (explaining the purpose, risks, type of research and researcher responsibilities) before beginning any research trial. In less developed/poor countries additional concerns make ethical consent requirements challenging at best. For instance, illiteracy rates are higher and the quality of secondary care available during the trial is low due to the lack of medical supplies and diagnostic equipment. There may also be inadequate oversight from patient safety review boards as well as the danger that patients may be coerced by foreign officials to participate in these research trials. Fraud and data integrity are also significant concerns due to the limited governmental oversight and weak regulations in these countries.

Some possible solutions

Reducing Bureaucracy

In honor of the 1742 scurvy trials by James Lind, May 20, 2005 marked the first International Clinical Trials Day. This day recognizes that biomedical research can only be done as a partnership between the medical profession and the public. This partnership can be especially helpful when we consider the bureaucratic challenges researchers face in conducting clinical trials.

Vast bureaucratic requirements have created an environment in which it is harder to conduct research. While many of these practices are part of an effort to protect research participants, it is imperative that researchers and the public work together to streamline extraneous requirements so that we may all benefit from the proven successes of clinical trials, namely cheaper, safer, and more effective treatments, longer life expectancies, and better quality of life.

Clinical trial registry

Clinical research for the benefit of patients is the overarching objective of the World Health Organization's (WHO) effort to institute a universal registry for clinical trials. To this end, the International Clinical Trials Registry Platform (ICTRP) based at WHO, has worked to formulate a minimum trial registration dataset of 20 items for all trials.⁷ This sets an important global ethical standard for all who are involved in clinical research. Key contributors to this initiative include the US National Library of Medicine's ClinicalTrials.gov (<http://clinicaltrials.gov>) and the UK's International Standard Randomised Controlled Trial Number (ISRCTN) register (<http://controlled-trials.com/isrctn/>),

and the Australian Clinical Trials Registry at the NHMRC Clinical Trials Centre (<http://www.ctc.usyd.edu.au/>).⁸ Groups such as the International Committee of Medical Journal Editors (ICMJE) have also instituted policies requiring trial-registration before being considered for publication.⁹

Revisiting Ingelfinder

In the past, medical journal editors have criticized pharmaceutical companies in their pre-publication disclosure of results. Adhering to what is known as the Ingelfinder Rule, most editors consider a manuscript for publication only if its substance has not been submitted or reported elsewhere. Given the accessibility of information in this electronic age, and the ethical appropriateness of sharing important trial results as quickly and as wide-spread as possible, the Ingelfinder rule may be outdated. Journals could require that information from domestic and foreign trials be submitted to the trial results bank before publication. As Horton advocates, "This mechanism would not compromise the publication process but would only add to transparency—helping to secure trust and credibility in the global clinical trials enterprise, an objective vital to patient's interests."¹⁰

Unresolved issues: A time for renewed action

While great strides have been made addressing issues of ethics, fraud, and data quality, perhaps it is now time for the research community to tackle the yet, unresolved broader issues.

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- Only 1% of new drugs approved between 1975-1999 were specifically developed for tropical diseases and tuberculosis which account for 10 % of the global disease burden.¹¹
- Although development of drugs and therapies for these conditions has waned, 14 million poor people die from infectious diseases each year, predominantly in developing countries¹¹.
- Most of the world's 40 million people with HIV/AIDS live in the developing world.¹²
- The poor also dominate non-communicable disease tables, accounting for 59% of the 56.5 million annual global deaths.¹³

In spite of these alarming statistics, the pharmaceutical industry and others involved in clinical research decidedly move in a different direction. For example, twice as much is spent on marketing a drug as on its research and development.¹⁴ Further, 68% of all NCEs sold worldwide in the last 25 years and the vast majority approved in the US in 2002 were "me-too drugs" - modified mimics of existing medications that offer little or no therapeutic gain.^{15, 16}

It is time to revisit the health needs-driven approach to drug discovery.¹⁷ International treaties can help shift the discourse

from trade and profit to health, the development of affordable medicines, and a prioritization of neglected diseases. While such a new international treaty on health research and development could provide a framework to redirect our scientific expertise to priority health needs, moving such a document forward is not without difficulties. It is also paramount that any solution includes and addresses issues such as the “therapeutic misconception” (whereby patients conclude trial participation emphasizes their personal health rather than scientific progress) and cultural factors that must balance individual participation with the participants’ responsibilities to their family and communities.

Even more importantly, we must ensure access to post-trial benefits for participants in developing nations. In the poorest countries of the developing world few health care services are available and if so, are sorely limited. In today’s world of international clinical trials, even if proven safe and effective, most new medications are likely to be too expensive for patients in poor developing nations. Withholding these drugs, either by omission or commission, would then provide no real long-term benefit for the very people who helped test them. Whether a new

drug, device or other experimental intervention, it should be our ethical imperative to sustain an appropriate level of trust between participants and researchers by continuing an efficacious intervention following the completion of the clinical trial. Anything less than this is akin to letting a youngster who is helping bake a cake, lick the spoon while preparing and mixing the batter but not giving him or her a piece of the cake once it comes out of the oven.

Although many would argue that given the global inequities in wealth and resources, clinical trials researchers, whether governmental or industry-based, have no ethical obligation to make drugs, equipment, treatment or other resources available to members of the broader community or host country, perhaps it is time to rethink our stance. In an ever-shrinking world, we can no longer use the human resources of developing countries without giving something in return. Rather than simply sharing a piece of that baked cake with the youngster, why not share the dessert with the entire family, or even the entire neighborhood? This type of altruism would demonstrate a collective concern for the welfare of their entire community and help promote a sense of global solidarity. Shouldn’t this be a goal of a caring society? ●

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