Outsourcing clinical trials

In parallel with the increase in medical tourism, the pharmaceutical industry has embraced globalization and is rapidly expanding clinical trials to countries outside North America and western Europe. Glickman and colleagues discuss trends in globalization and consider a series of ethical and scientific questions raised by the expansion of clinical research into developing countries in their recent article (Glickman, S. W. *et al. N. Engl. J. Med*. 360, 816–823 [2009]). The authors explore the issues of who benefits from globalization of clinical trials, the potential for exploitation of trial participants, and whether trial results are accurate, valid and can be extrapolated to other settings.

The statistics on the economics of clinical trials are astounding. While the number of FDA-regulated investigators in the US has declined by 5.5% since 2002, the number based outside the US has increased by 15%. Approximately one-third of the trials registered on http://clinicaltrials.gov/ are now conducted exclusively outside the US and over half of all study sites are now outside the US. The shift towards conducting trials in eastern Europe, South America, India and China is related to issues of costs and regulatory hurdles, which have become intertwined. Labor costs (physicians, nurses and coordinators) can be up to 90% lower outside the US, and costs associated with the time required to recruit participants and conduct a trial are reduced by the availability of large pools of potential participants who, by virtue of economic considerations, social status or health systems, may not have access to optimal therapies outside of clinical trials. Furthermore, regulatory barriers to performing clinical trials in North America and western Europe are becoming increasingly bureaucratic and expensive: the costs of performing clinical trials now surpass federal funding for clinical research.

The benefits of conducting trials in developing countries include cost-efficient evaluations of efficacy and safety of drugs or devices, and fostering global relationships among clinicians, and between clinicians and industry. However, the ethical and scientific questions raised by such trials are substantial and interconnected. As Glickman and colleagues note in their article, the rights of trial participants may be jeopardized by "disparities in education, economics, social standing, and health care systems" if they do not understand the investigational nature of the products being tested or the implications of placebo controls, receive a disproportionate financial compensation for participation, or have limited access to alternative therapies. Furthermore, the possibility that Institutional Review Board oversight and discussions of informed consent might not performed according to the standards of developed countries is a matter of concern.

Scientific issues related to the 'outsourcing' of clinical trials include the need for transparency with regard to access to data, and publication rights for investigators from developing countries who might be inexperienced in trial design, implementation, and analysis (and consequently may have little marketing or intellectual clout with the sponsor). Other concerns relate to populations of patients enrolled in clinical trials. Does the trial respond to or prioritize the health needs of the country or region? After the study ends, will patients have access to the best proven therapy identified by the trial, as expected by the Declaration of Helsinki? Are the results applicable to other populations with regard to genetic diversity or baseline characteristics (many patients enrolled in developing countries differ from their counterparts in developed nations in relation to disease stage or concomitant therapies)? Is the ethical conduct of the trial undermined by financial incentives for investigators (an issue that also applies to developed countries)?

I am aware of numerous examples of divergent outcomes from clinical trials performed in different settings, or even in similar settings but with demographically different populations of patients. Results from phase II trials are generally much more optimistic than phase III results. Placebo responses vary among different populations. The clinical trial setting (hospital versus outpatient, academic center versus private clinic) requires scrutiny as to whether results can be extrapolated to other groups of patients. Indeed, some therapies that are approved by regulators in one country have not been similarly viewed as safe and effective in others.

Glickman and colleagues have outlined a series of proposals to address these issues. Basically, a greater degree of global harmonization is required, and not just between North American and European regulatory agencies and industries. We need to create formal programs for the training of investigators, to enable further standardization of clinical trial operations, analysis and publication, and to support uniform monitoring and protection of the rights of trial participants.

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Competing interests
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