

## Virtual Mentor

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### JOURNAL DISCUSSION

#### Clinical Research in Low- and Middle-Income Countries

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**Glickman SW, McHutchison JG, Peterson ED, et al. Ethical and scientific implications of the globalization of clinical research. *N Engl J Med.* 2009;360(8):816-823.**

Glickman et al. offer a thoughtful discussion of the ethical and scientific implications of what they term the globalization of clinical research [1]. Globalization is relevant to the bioethics of international clinical research, the authors say, because it has changed the way that clinical research is conducted. They identify various “push” and “pull” factors that have resulted in more research being conducted in developing countries—a collective term for countries that are not part of the traditional “developed world,” where the latter term signifies the United States, Canada, Australia, New Zealand, and the countries of the European Union. What the former term hides, however, is the fact that socioeconomic development is a dynamic process and that developing countries are diverse and marked by variance in degrees of socioeconomic development.

To take an extreme example, according to the World Bank, the term “developing countries” encompasses those as underdeveloped as Sierra Leone and those as sophisticated as Turkey—a country with a credible chance of attaining full membership status in the European Union in the near future. It therefore may have been helpful if Glickman et al. had stated more specifically which developing countries they had in mind. Were they referring to middle-income countries such as India, Thailand, Argentina, and Turkey, in which medical infrastructure is relatively strong, life expectancy is increasing, and prevalence of Western-developed chronic diseases is growing, or to low-income countries (the majority of which are located in sub-Saharan Africa) in which life expectancy frequently lags behind that of fully developed countries by decades and in some cases has fallen from peaks seen 30 years ago? This distinction is important because countries like India and Thailand, although still dogged by traditional poverty-related diseases such as tuberculosis and malaria, are also witnessing rapidly increasing incidences of industrial diseases, such as cardiovascular disease, malignancies, diabetes, and obesity. In those countries and others like them, clinical research into interventions for these developed-world diseases is relevant and important. One suspects that the authors were referring to the middle-income countries, since the standards required of research for licensure of new products in the United States, Australia, New Zealand, and the European Union demand a degree of medical knowledge, skill, and infrastructure sophistication not available in the poorest and least-developed countries of the world.

If one accepts this middle-income interpretation of “developing countries,” some aspects of the Glickman et al. article become contentious. It is most pronounced when they discuss the ethical and scientific questions raised by globalization. This section describes a major concern with the ethical oversight of research involving human subjects in developing countries and goes on to imply that standards of Australia’s Human Research Ethics Committee (HREC) are not sufficient to reasonably protect the rights of individuals enrolled in clinical trials in those countries. They also state that, because the standards of care differ in developing countries, some trials may be allowed there that would be rejected as “unethical” in developed countries. This raises the question of who is better able to define ethical standards for conduct of clinical trials in a given country—members of HRECs in that country or members of HRECs in high-income countries?

The authors recount a debate predominantly conducted in the *New England Journal of Medicine* about studies conducted in low- and middle-income countries to test the efficacy of AZT in preventing mother-to-child transmission of HIV infection. A placebo was used in those trials despite evidence produced in the United States that AZT was effective [2]. The rationale for a placebo-controlled study was that the means of drug delivery, length of administration, and cost of the particular course of AZT validated in the original U.S. study were prohibitive and impractical in developing countries. The debate centred on whether administration of placebo was ethical given the unequivocal benefit of AZT demonstrated in the United States. Much heat was produced on both sides of the argument, but less light was shed on either clearly defining the issues or searching for rational answers. The debate continues [3].

It cannot be denied that pharmaceutical companies in particular have found it increasingly attractive to take their research protocols to middle-income countries, and Glickman et al. identify and discuss the key factors contributing to this trend. Clearly, cost is a major factor; as the authors state, the cost of labour even in middle-income countries such as China and India is markedly lower than in high-income countries. In addition, the regulatory burden associated with the conduct of clinical research in high-income settings like the United States and the European Union increases costs further. The clinical research enterprise, like other industries, seeks best value for money and maximisation of profit.

Concluding their article with a look at the next steps, the authors state, “...the goal is to foster innovation and access to therapies while ensuring that clinical research is conducted in populations in proportion to the potential uses of the products after approval” [4]. This definition is controversial and arguable. It is improbable that an agency could measure whether research conducted in a particular population was proportionate to the potential uses of the products by that population after approval. The goal fails to recognise that a country’s development is dynamic. As the current economic crisis is constantly reminding us, the economic situation of countries can change—who would have imagined 30 years ago that the United States would need a

major government-led stimulus package to boost its economy, or that Singapore would be classified as a high-income nation?

The article is dominated by an analysis of pharmaceutical-industry-sponsored clinical research, an industry that a number of commentators argue harbours a fundamental conflict between its duty to serve its shareholders and its service to the public health [5]. There are alternative models, however, and one will be outlined in the following section.

### **An Alternative View**

The goal of research is to improve health through the advancement of knowledge [6]. Ethical clinical research consists of improving the strength of the evidence base (knowledge) to bring greater health benefits to human populations regardless of their development status. The increasing presence of clinical trials in developing countries reflects the essential fact that such countries represent important growth areas for pharmaceutical companies and clinical research organizations. It also demonstrates growing confidence that a developing country's health infrastructure can reliably perform at the standard needed to comply with the requirements of the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP).

The Therapeutic and Vaccine Research Program of the National Centre in HIV Epidemiology and Clinical Research (NCHECR) (our academic clinical research centre) has been developing an alternative model to the conduct of clinical research over the last decade or so, which in many respects fits the model described by Glickman et al. in their Next Steps section. This model takes a collaborative public-and private-institution approach to clinical research that builds partnerships between various entities such as the pharmaceutical industry, academic centres, and charitable institutions to broker international, multicentre research protocols. Protocol development is guided by an iterative, consultative process with our academic centre that maintains prime responsibility for trial design. This responsibility also extends to data quality control, data capture and analysis, manuscript authorship, and decisions about publication, thereby protecting the independence of the research.

The collaborative model can attend to the partner sites' research needs, including the design, conduct, and ethical oversight of trials. A protocol steering committee (PSC) has been formed with broad representation from partners, including an investigator-representative from each country that has at least one site and at least one patient enrolled. The sites are selected on the basis of their expressed interest in joining the network and the results of a field review from NCHECR staff in which the capacity of the site to collaborate successfully in following the protocol and capturing and transmitting clean data to a central database is assessed. The NCHECR works with sites that need assistance to meet the network's standards. The research protocol is executed by an independent management team at the NCHECR, which reports directly to the PSC. Through experience, some sites reach a point where they are able to act as independent coordinating centres, taking responsibility for assuring the

quality of the research conducted among their geographically clustered group and reporting to our central site.

We believe that this model offers a number of advantages, from the independence and reliability of the results to the potential benefit for partner academic institutions and health care personnel in developing countries. We believe these latter opportunities are many and include the following: (1) development of centres of research excellence that become centres of academic education, training, and clinical service; (2) establishment of best-practice institutions; (3) a means by which other collaborative institutions can meaningfully interact, fostering productive North-South as well as South-South relationships; (4) a means for knowledge and technology transfer to be successfully performed, guided, and sustained; (5) access to care and the ability for health care workers to become familiar with the use of new products; (6) a model of capacity building that may be influential in building up health infrastructure capacity in general.

Ultimately, the implementation of clinical research and establishment of clinical research centres of excellence in developing countries makes it possible to conduct locally and internationally relevant studies that help build and inform evidence-based guidelines and health policy decisions. It can be reasonably hoped that data gathered from international, multicentre clinical research can inform guidelines for conduct of research in accord with what Glickman et al. refer to as the social ecology and genetic makeup of trial populations [7].

### **Take-Home Messages**

- The term developing countries is not always a helpful one, inasmuch as it obscures marked differences in development status between low-income and middle-income countries. In general, the movement of clinical research to developing countries has actually been a movement to middle-developed countries.
- Clinical research is moving to countries where the research industry gets the best value for money while gathering data acceptable for submission to regulatory agencies. While conflict of interest may seem unavoidable, this movement is driven by market forces that are difficult to stop. Research prospectively viewed as undesirable by various interested parties in high-income countries is usually welcomed by those same parties in middle-income countries.
- One of the most vexing ethical issues in clinical research is that of the appropriate standard against which one measures the value and burden of an intervention, particularly in middle- and low-income countries. It is often an emotive and divisive issue that demands thought and a willingness to consider all reasonable arguments carefully.
- Rather than lament the shift of clinical research to middle-developed countries, it may be more fruitful to see the trend as an opportunity to create collaborations which might benefit all.

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