

## SOUNDING BOARD

## Ethical and Scientific Implications of the Globalization of Clinical Research

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Economic globalization is an important development of the past half century. Proponents of globalization highlight the benefits of greater economic growth and prosperity; critics point to the exacerbation of economic disparities and the exploitation of workers, particularly in developing (i.e., low- and middle-income) countries.<sup>1,2</sup> Pharmaceutical and device companies have embraced globalization as a core component of their business models, especially in the realm of clinical trials. This phenomenon raises important questions about the economics and ethics of clinical research and the translation of trial results to clinical practice: Who benefits from the globalization of clinical trials? What is the potential for exploitation of research subjects? Are trial results accurate and valid, and can they be extrapolated to other settings? In this article, we discuss recent trends in and underlying reasons for the globalization of clinical research, highlight important scientific and ethical concerns, and propose steps for the harmonization of international clinical research.

### TRENDS IN THE GLOBALIZATION OF CLINICAL RESEARCH

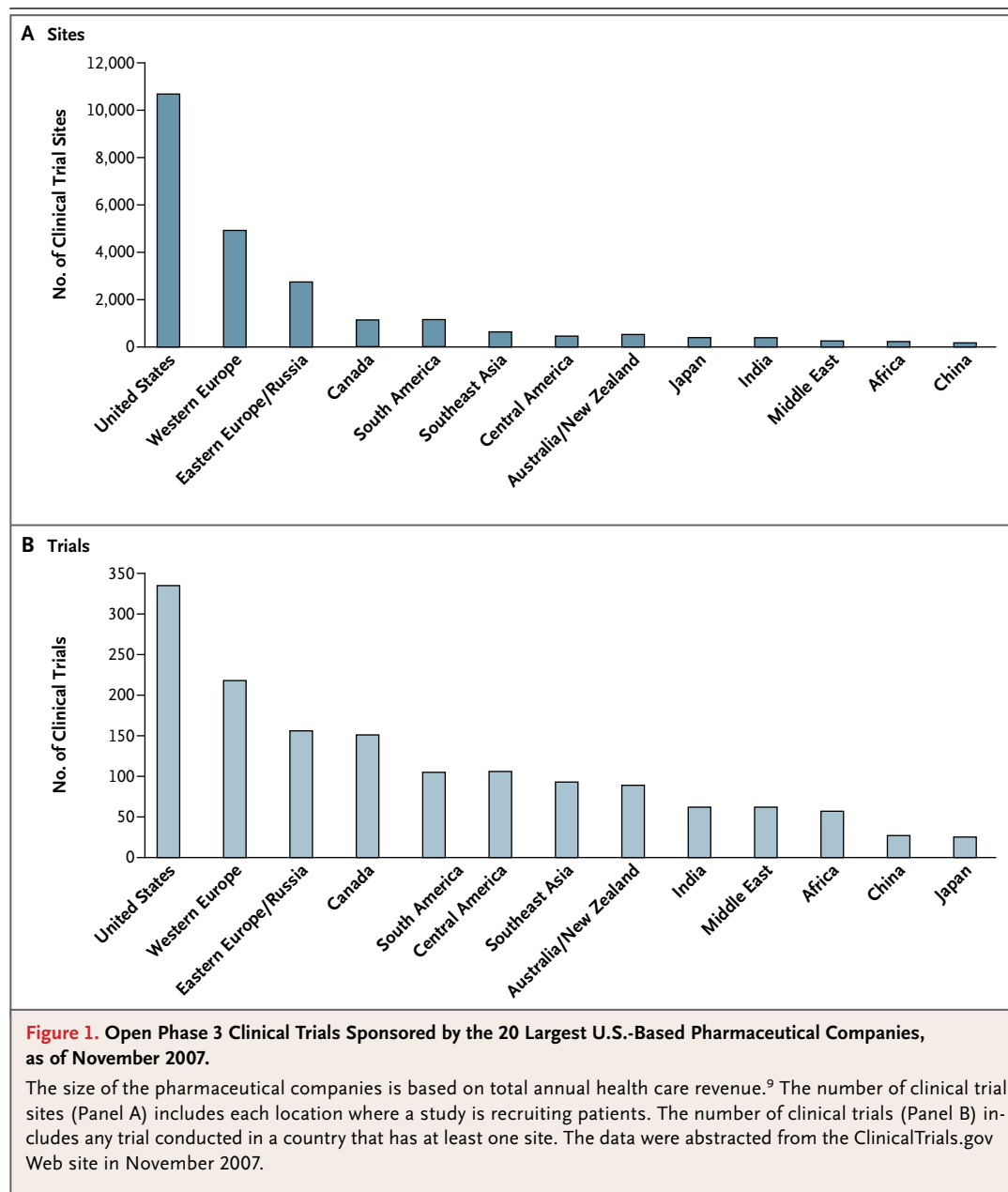
Clinical trials increasingly occur on a global scale as industry and government sponsors in wealthy countries move trials to less wealthy countries.<sup>3-8</sup> Since 2002, the number of active Food and Drug Administration (FDA)-regulated investigators based outside the United States has grown by 15% annually, whereas the number of U.S.-based investigators has declined by 5.5%.<sup>3</sup> This trend suggests that clinical research is undergoing the same globalization process as other industries. To further explore this trend, we used the ClinicalTrials.gov registry to examine recruitment

in industry-sponsored phase 3 clinical trials as of November 2007 for the 20 largest U.S.-based pharmaceutical companies.<sup>9</sup> We found that approximately one third of the trials (157 of 509) are being conducted solely outside the United States and that a majority of study sites (13,521 of 24,206) are outside the United States. Many of these trials are being conducted in developing countries, including the rapidly evolving countries of Eastern Europe and the Russian Federation (Fig. 1).

The globalization of clinical research is also a relatively recent phenomenon. We reviewed 300 articles reporting the results of clinical trials in the *New England Journal of Medicine (NEJM)*, the *Lancet*, and the *Journal of the American Medical Association (JAMA)* in 1995 and 2005 and found that the number of countries serving as trial sites outside the United States more than doubled in 10 years, whereas the proportion of trials conducted in the United States and Western Europe decreased (Table 1).

What has led to this dramatic shift in the location of clinical trials? One explanation is that pharmaceutical and device companies can realize substantial cost savings by conducting trials in developing countries, so they are increasingly moving phase 2 and phase 3 trials to places such as India and South America.<sup>10,11</sup> A pharmaceutical executive reported that a first-rate academic medical center in India charges approximately \$1,500 to \$2,000 per case report, less than one tenth the cost at a second-tier center in the United States.<sup>10</sup> Since clinical research costs are driven by human labor, much of this cost difference is attributable to the lower salaries of physicians, nurses, and study coordinators in developing countries.<sup>12</sup>

Globalization of clinical trials may also shorten the timeline for clinical testing. In 2000, the



cost to develop a new drug averaged \$802 million, with time costs accounting for half of that amount.<sup>13</sup> The large pool of potential research participants and the lower cost of research in countries such as China and India provide opportunities to accelerate recruitment.<sup>6,14,15</sup> Clinical testing in developing countries is also attractive to pharmaceutical and device companies because it can help them overcome regulatory barriers for drug approval in these countries in which the population size alone offers the promise of expanding

markets.<sup>16</sup> Widespread adoption of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice (ICH-GCP) guidelines and stronger intellectual property protections in developing countries may also have contributed to the globalization of clinical research.<sup>11</sup>

An important force that is moving clinical trials to developing countries is the increasingly bureaucratic and expensive regulatory environ-

**Table 1. Characteristics of 300 Clinical Trials Reported in the *Journal of the American Medical Association*, the *Lancet*, and the *New England Journal of Medicine* in 1995 and 2005.\***

Characteristic	Year	
	1995 (N=150)	2005 (N=150)
No. of countries represented	33	70
No. of patients per trial		
Median	215	661
Interquartile range	75–830	239–1837
Multinational trials — no. (%)	25 (16.7)	44 (29.3)
Information reported about location — no. (%)		
Locations not reported	59 (39.3)	13 (8.7)
Only continents reported	5 (3.3)	8 (5.3)
Only number of countries reported	6 (4.0)	14 (9.3)
Names of countries reported	79 (52.7)	113 (75.3)
Enrollment from each country reported†	1 (4.0)	2 (4.5)
Countries per trial — no. (%)‡		
1	65 (75.6)	94 (72.9)
2–10	17 (19.8)	20 (15.5)
11–20	4 (4.7)	5 (3.9)
>20	0	10 (7.8)
Regions represented — % of trials		
Africa	5.0	8.7
Eastern Europe and Russia	2.5	5.2
Middle East	1.3	3.5
Asia	8.8	6.1
United States	53.8	42.6
Western Europe	40.0	36.5

\* Percentages may not sum to 100 because of rounding.

† The percentages are based on 25 multinational trials in 1995, and 44 in 2005.

‡ The percentages are based on the number of articles that reported country-level information (86 articles in 1995 and 129 articles in 2005).

ment in many wealthy countries. Regulations governing the conduct of clinical research have become more and more complex, placing a greater burden on investigators in terms of compliance, documentation, and training.<sup>17–20</sup> In the United States, the costs of conducting clinical trials have generally outstripped federal funding for clinical research and strained industry's site-level research budgets.<sup>18</sup> Although these regulations are well intended, they are generally uncoordinated and frequently have not been subjected to empirical study to determine which elements improve the conduct of trials and which elements add cost

without benefiting participants or the research mission.<sup>21–23</sup>

#### ETHICAL AND SCIENTIFIC QUESTIONS RAISED BY GLOBALIZATION

There are clear benefits to conducting trials in developing countries. These include fostering positive relationships among clinician investigators globally and answering questions about the safety and efficacy of drugs and devices that are of interest throughout the world.<sup>20</sup> At the same time, the globalization of clinical trials raises ethical and scientific concerns.<sup>14,24</sup> Regulatory bodies are often structured to monitor the quality of clinical trial data and the safety of drugs and devices in their domestic markets. They have limited information on many aspects of research conducted outside their jurisdictions or countries, including the sites, investigators, and participants and the quality of trial data.<sup>5,25</sup> Thus, we know little about the conduct and quality of research in countries that have relatively little clinical research experience.

A major concern is the ethical oversight of research involving human subjects in developing countries. Wide disparities in education, economic and social standing, and health care systems may jeopardize the rights of research participants.<sup>26–28</sup> There may be a relative lack of understanding of both the investigational nature of therapeutic products and the use of placebo groups.<sup>29</sup> In some places, financial compensation for research participation may exceed participants' annual wages, and participation in a clinical trial may provide the only access to care for persons with the condition under study.<sup>30,31</sup> Standards of health care in developing countries may also allow ethically problematic study designs or trials that would not be allowed in wealthier countries.<sup>32–38</sup> In one study, only 56% of the 670 researchers surveyed in developing countries reported that their research had been reviewed by a local institutional review board or health ministry.<sup>39</sup> In another study, 90% of published clinical trials conducted in China in 2004 did not report ethical review of the protocol and only 18% adequately discussed informed consent.<sup>40</sup>

Another concern is the transparency of clinical research in developing countries. The International Committee of Medical Journal Editors has issued guidelines for investigators with regard

to participation in study design, access to data, and control over the publication of results.<sup>41</sup> Protection of publication rights for investigators is necessary to the transparency and integrity of research, yet it is an ongoing area of contention for industry sponsors.<sup>42,43</sup> Investigators in developing countries are generally less experienced and less familiar with these guidelines and, therefore, less likely to have access to trial data or to publish results.<sup>44,45</sup>

To what extent should people in developing countries be enrolled in clinical trials? Clinical research should be responsive to the health needs and priorities of the communities in which the research is conducted.<sup>46</sup> Given the increasing global prevalence of conditions such as cardiovascular disease, it will be important to test drugs and devices on a global scale. However, among the ongoing phase 3 clinical trials that we examined that were sponsored by U.S.-based companies in developing countries, none were trials of diseases such as tuberculosis that disproportionately affect the populations of these countries. In contrast, we found a variety of trials in developing countries for conditions such as allergic rhinitis and overactive bladder. Developing countries will also not realize the benefits of trials if the drugs being evaluated do not become readily available there once they have been approved. The Declaration of Helsinki expresses an expectation that every patient enrolled in a clinical trial should, at the end of the trial, be assured access to the best proven therapy identified in the study.<sup>47</sup> The reality is that the overwhelming majority of drugs for the treatment of common diseases are sold in the wealthiest countries.<sup>48</sup> Therefore, we need to confirm whether the growth in clinical trials worldwide is accompanied by greater availability of drugs in the countries where the trials are conducted.

To the extent that there is an imbalance between clinical trials in developing countries and the extrapolation of results to populations in developed countries, additional questions arise: What is the nature of the health care delivery system of the country where the trial was conducted? Do social ecology and the genetic makeup of the study population allow trial results to be generalized to populations in which the treatment will most likely be used?

Hospital and clinic infrastructure, treatment choices, and quality of care vary widely from coun-

try to country. We would not expect, therefore, that access to medications or devices alone, without appropriate physician training and health care infrastructure, would have the same effect on disease as would use of the same therapy in a state-of-the-art clinical practice. In large clinical trials, physician training, practice patterns, and medical infrastructure are generally not reported at the site or country level. Thus, it is difficult to assess whether standards of care are similar among study sites or whether they are similar among countries. Patients in developing countries often have untreated or undertreated diseases, providing a greater opportunity to recruit for clinical studies patients who have not previously received treatment, rather than patients whose diseases are refractory to treatment.<sup>49,50</sup> The practice of recruiting patients who have not previously received treatment suggests that new products are increasingly being evaluated under circumstances that are not generalizable to most patients in developed countries. For patients who are already receiving multiple effective therapies for a condition, it remains unclear whether adding a new agent would be beneficial, neutral, or detrimental on the basis of the findings of a successful placebo-controlled trial in a population of patients who have not previously received treatment.

Interaction effects according to treatment and country were discussed at a 2007 meeting of the FDA Cardiovascular and Renal Drugs Advisory Committee about a drug for atrial fibrillation.<sup>51</sup> The panel raised concern about the applicability to the United States of the phase 3 trial results under discussion, since more than 90% of the patients enrolled in the trial were from Eastern Europe. In our review of articles reporting trial results that were published in *NEJM*, *JAMA*, and the *Lancet* in 2005, less than 5% of the multinational trials reported study recruitment numbers according to individual country (Table 1).

The second question relates to social ecology and the genetic makeup of trial populations. Geographically distinct populations can have different genetic profiles, and these differences have been shown to be related to the safety and effectiveness of drugs and even medical devices. For example, a study of 42 genetic variants associated with pharmacologic response in drug studies showed that more than two thirds had significant differences in frequency between persons of African ancestry and those of European ancestry.<sup>52</sup>

In another study, a common mitochondrial polymorphism associated with impaired ethanol metabolism and decreased efficacy of nitroglycerin treatment<sup>53</sup> was found almost exclusively in populations of Asian origin, including 40% of persons of East Asian origin.<sup>54</sup> This finding may affect the relevance of trials involving cardiac, circulatory, and neurologic disorders that are treated with nitroglycerin or nitric oxide–dependent therapies.<sup>55</sup> Genetic diversity is often not considered in study design and interpretation and in the reporting of trial results.

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#### NEXT STEPS

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In our opinion, multiple approaches are needed to address concerns raised by the globalization of clinical research (Table 2). In general, 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. Also, it is essential to create a robust framework to ensure the integrity of research, wherever it takes place.

The complexity and cost of clinical research in developed countries are recurring concerns. A careful effort to streamline regulations governing clinical trials could reduce redundancy in the system while ensuring ethical conduct. Improved research efficiency would decrease the differential costs of research among countries and increase the likelihood that trials are initiated in the countries where the drugs being tested will be sold. Greater use of centralized institutional review boards, standard terms for research contracts, and the development of streamlined best practices to reduce unnecessary work for investigators and medical institutions are needed.<sup>29,62</sup>

The ICH-GCP guidelines are valuable regarding the technical standards and ethical oversight of clinical trials.<sup>56</sup> However, certain guidelines, such as the one indicating that sponsors should ensure that trials are “adequately monitored,” are subject to interpretation and are only as effective as the degree to which they are implemented. The solution is not simple; different types of trials require different monitoring procedures. A rigid set of rules will not suffice and may even impair the quality of the research<sup>23,45,62</sup>; instead, a vast improvement in the quality of clinical research is needed, so that trial procedures match the research goals and societal needs.

Industry sponsors, contract research organizations, and the academic community can meet the challenges of globalization by accepting full responsibility for the ethical conduct and quality oversight of these trials. Key strategies for clinical trials should be outlined in formal clinical-development plans, publicly vetted, and submitted to regulatory agencies. The plans would outline the anticipated study design, the choice and justification of trial sites, and mechanisms for ensuring the quality of the clinical trial, including independent oversight and site evaluation and monitoring. Sponsors of multinational research should also be required to document that study sites are determined on the basis of anticipated product availability after approval.

Improved international collaboration among academic investigators would increase the quality of multinational trials. Investigators in developing countries would benefit from rigorous training in the design, conduct, and ethical oversight of trials, which would allow them to engage more fully in multinational clinical research at a leadership level. These programs could be structured as courses of study in either residence or distance offerings through academic institutions and jointly funded by industry and clinical research organizations. In addition, an international mechanism for tracking investigators who are trained through such programs or, conversely, who have been prohibited from conducting clinical studies is needed.

Transparency of the conduct and results of clinical trials contributes to the integrity of clinical research. Accordingly, provisions for the publication of all clinical trial data and protection of publication rights for investigators should be preserved, independent of sponsorship. The characterization of trial populations and trial sites in publications and registries should be improved, and enhanced international efforts to collect and analyze pharmacogenomic data are needed. This information will help identify therapies that benefit populations in all parts of the world and will better enable local regulatory bodies to interpret the relevance of trial results from other countries for their target populations.

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#### CONCLUSIONS

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Long-term solutions to problems arising from the globalization of clinical research will require input from stakeholders in academia, industry, and

**Table 2. Issues and Proposed Solutions for the Globalization of Clinical Research.\***

Issue	Problem	Proposed Solutions
Selection of patients in multinational trials	Research in communities that are not intended to be major markets for the products under testing can be ethically problematic.	Sponsors need to describe how trial populations match their intended markets for the drugs or medical devices being tested. Create target enrollment of patients according to geographic region on the basis of the intended use of the product, similar to FDA and NIH policies for target enrollment of women and minorities in clinical trials.
Transparency of clinical trial results in developing countries	Protection of publication rights and access to trial data for investigators is necessary to preserve the integrity of research.	Publish all clinical trial data regardless of the location of research, and reinforce these requirements according to the FDA Amendments Act of 2007. Preserve publication rights of investigators globally, independent of sponsors, through legal agreements at the onset of the clinical trial. Create mechanisms for leadership of clinical trials that incorporate representatives of key countries involved in the study.
Regulatory oversight of international clinical research	Regulatory agencies in many developed countries have limited information on important aspects of clinical trials that are conducted outside their countries, including sites, investigators, participating subjects, and ancillary health treatments that affect trial outcomes.	Create a formal mechanism for sharing regulatory oversight governing the conduct of clinical studies between government agencies on a global basis. Create a public registry of IRBs and an inventory of country-specific provisions for the ethical oversight of clinical research. Conduct a comprehensive study of issues related to the globalization of clinical research by the Institute of Medicine or the World Health Organization. Develop a central statistical monitoring system to find unusual data patterns in trial results that raise suspicion of fraud.
Training and experience of clinical investigators globally	Clinical investigators in developing countries are typically less experienced in conducting clinical trials than are those in developed countries.	Create formal training programs for clinical research and ethics for investigators in developing countries to expand their global clinical research leadership capacity and improve collaboration between academic investigators worldwide. Create a mechanism for tracking investigators who are formally trained to conduct clinical trials as well as those who have been prohibited from conducting such studies.
Genomic information in drug development	Lack of pharmacogenomic information for trial subjects limits confidence in the generalizability of results.	Expand the FDA Voluntary Genomic Data Submissions program <sup>56</sup> to international regulatory agencies and develop global data-warehousing and data-analyzing capabilities.
IRB quality and efficiency	Redundancy in the review process may harm patient safety by requiring diversion of effort to unnecessary procedures and practices. <sup>39</sup>	Make greater use of centralized IRBs (e.g., Central Institutional Review Board Initiative <sup>57</sup> and European Union Clinical Trials Directive <sup>58</sup> ) or encourage mutual acceptance of the review of proposals in consortia (e.g., Biomedical Research Alliance of New York <sup>59</sup> ) and develop streamlined best practices to reduce unnecessary work for investigators (e.g., Clinical Trials Transformation Initiative <sup>60</sup> ).
Payment compliance	Increased costs and delays associated with payment for clinical research subjects divert financial support from research to administration and make research less attractive to investigators because of the risk of criminal penalties from errors.	Establish a nonpunitive mechanism for reconciliation of payment for clinical research subjects and expand mechanisms to pay for usual care services for trial participants (e.g., within Medicare and Medicaid in the United States).
Commercial contracts	The variety of contracting practices brings complexity and delays to research.	Adopt standard contract language for clinical research agreements. <sup>61</sup>
Confidentiality agreements in commercial contracts	Confidentiality agreements reduce the transparency and efficiency of clinical research.	Adopt standard confidentiality agreements for clinical trials.

\* FDA denotes Food and Drug Administration, IRB institutional review board, and NIH National Institutes of Health.

regulatory agencies around the world. The future of the pharmaceutical and device industries is predicated on addressing these issues. A comprehensive review including representatives from developed and developing countries, perhaps commissioned by the Institute of Medicine or the World Health Organization, is needed to reach international consensus on these issues. We must ensure the ethical and scientific integrity of clinical research globally, promote harmonization of international research, and provide information about the benefits and risks of new drugs and devices in the populations and environments in which patients live, wherever they may be.

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