Ethical and Scientific Implications of the Globalization of Clinical Research

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India's poor often test drugs bound for U.S. markets

Kris Hundley, Times Staff Writer
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Chandrika Dodiya shares a three-room home in the slums of Ahmedabad with seven family members. Her 28-year-old husband, Mukesh, earns about 7,000 rupees ($140) a month but briefly doubled his pay by volunteering to test a new drug for leg cramps. The trial left him with headaches, fever and lingering concerns. "Your life expectancy goes down if you do lots of trials," Mukesh says.

[KATHLEEN FLYNN | Times]

Reporting a story on drug studies in India recently, I had plenty of interviews with people at the top. Doctors, government officials, entrepreneurs who make their living running clinical trials leaned over polished conference tables in modern, air-conditioned offices in some of India's biggest cities. They assured me that India is capable of running world-class studies on new medicines destined for the U.S. market. No problem.

But finding the people at the bottom rung, those testing the drugs or the experimental procedures, was more difficult. They are all around you, yet they are invisible. They are often poor and illiterate. If something goes wrong in a trial, they don't hire a lawyer, they just go home. They disappear into a haze of patient confidentiality.

Source: http://www.tampabay.com/opinion/essays/article934654.ece

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Ethical and Scientific Implications of the Globalization of Clinical Research

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- Since 2002, the number of FDA investigators outside the US has grown by 15% annually, while the number inside the US has declined by 5.5%.
- One-third of phase 3 trials of the 20 largest US pharmaceutical companies are being conducted solely outside the US.
- For those same firms and studies, a majority of study sites (13,521 of 24,206) are outside the US.

Source: Glickman, SW et al. NEJM 2009

Why Is This Occurring?

- Factors pushing research outside US/EU/Japan
  - Cost
  - Patient interest/availability
  - Regulations
- Factors pulling research to Eastern Europe/Asia
  - Cost
  - Patient interest/availability
  - Regulations

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 the 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[56] 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.[39]	Make greater use of centralized IRBs (e.g., Central Institutional Review Board Initiative[57] and European Union Clinical Trials Directive[58]) or encourage mutual acceptance of the review of proposals in consortia (e.g., Biomedical Research Alliance of New York[59]) and develop streamlined best practices to reduce unnecessary work for investigators (e.g., Clinical Trials Transformation Initiative[60]).
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.[61]
Confidentiality agreements in commercial contracts	Confidentiality agreements reduce the transparency and efficiency of clinical research.	Adopt standard confidentiality agreements for clinical trials.

Source: Glickman, SW et al. NEJM 2009.

Selection of Patients in Multinational Trials

- Problem**: Research in communities that are not intended to be major markets for the products under testing can be ethically problematic**
- Solutions
  - Sponsors should describe how trial populations match intended markets
  - Create target enrollment according to region on the basis of intended use of product, similar to target enrollment of women and minorities

Source: Glickman, SW et al. NEJM 2009.

Transparency of Clinical Trial Results in Developing Countries

- Problem**: Protection of publication rights and access to trial data for investigators is necessary to preserve the integrity of research**
- Solutions
  - Publish all data regardless of research location, and reinforce requirements according to FDA Amendments Act of 2007
  - Preserve publication rights globally through legal agreements at onset of trial
  - Create trial leadership that incorporates representatives of countries involved in study

Source: Glickman, SW et al. NEJM 2009.

Regulatory Oversight of International Clinical Research

- Problem**: Regulatory agencies have little information on trials conducted outside their countries**
- Solutions
  - Mechanism for sharing regulatory oversight between government agencies worldwide
  - Public registry of IRBs and inventory of country-specific provisions for ethical oversight
  - Comprehensive study of the globalization of clinical research by IOM or WHO
  - Central statistical monitoring system to find unusual data patterns suspicious for fraud

Source: Glickman, SW et al. NEJM 2009.

Training and Experience of Clinical Investigators

- Problem**: Investigators in developing countries are typically less experienced than investigators in developed countries**
- Solutions
  - Formal training programs for clinical research for investigators in developing countries to expand global clinical research leadership capacity and improve collaboration worldwide
  - Mechanism for tracking investigators who are trained to conduct clinical trials and those who have been prohibited from conducting trials

Source: Glickman, SW et al. NEJM 2009.

Genomic Information in Drug Development

- Problem**: Lack of pharmacogenomic data for subjects limits confidence in generalizability of results**
- Solutions
  - Expand FDA Voluntary Genomic Data Submissions program to international regulatory agencies
  - Develop global data warehousing and data analysis capabilities

Source: Glickman, SW et al. NEJM 2009.

IRB Quality and Inefficiency

- Problem**: Redundancy in review process may harm patient safety by requiring diversion of effort to unnecessary procedures and practices**
- Solutions
  - Greater use of centralized IRBs (eg, Central IRB Initiative, European Union Clinical Trials Directive)
  - Mutual acceptance of proposal review in consortia (eg, Biomedical Research Alliance of New York)
  - Streamlined best practices to reduce unnecessary work for investigators (eg, Clinical Trials Transformation Initiative)

Source: Glickman, SW et al. NEJM 2009.

Summary

- Outsourcing of clinical trials is increasing, not necessarily tied to target market opportunities for products.
- How do we retain clinical research in the target markets for these products?
- What ethical and regulatory infrastructure is required for global clinical research?