I recently collaborated on a paper that addresses the ethical and scientific implications of the globalization of clinical research. My coauthors and I wanted to quantify how much clinical research is occurring in the United States, how much is occurring offshore, and the extent to which these statistics have changed. We learned the following.

Since 2002, the number of US Food and Drug Administration investigators outside the United States has grown by 15% annually, whereas the number in the United States has declined by 5.5%. One third of phase 3 trials by the then 20 largest US pharmaceutical companies were conducted completely outside the United States. Therefore, for pivotal clinical trials sponsored by United States–based pharmaceutical companies, the research is occurring offshore. For the same firms in those studies, the majority of the trial sites also are outside the US; clinical trials were once conducted primarily in the United States and Europe or Japan, but research is now migrating to newly emerging market economies, especially India and China. In this paper, we asked the obvious question: why is research moving offshore?

Two factors are pulling research offshore, and we cannot do much about these factors in the United States. The first factor is cost. J.P. Garnier, then chief executive officer of GlaxoSmithKline, said the cost per patient in India might be one tenth the cost in the United States. The second factor is related to availability of patients, untreated or undertreated, who might be more available in certain markets. The availability of patients could speed recruitment into clinical trials and reduce the time cost of research. The time cost of research is approximately one half of the cost to bring a new drug to market. In our paper, we discuss the administrative costs of clinical research abroad can decrease costs and the time required to bring a new product to market. A more interesting issue, however, is that drug developers are not required to match study populations to target markets. Do data from emerging market economies adequately represent the data needed to inform choices about which therapies are appropriate for patients in the United States? At some point, a potential local market exists in each of these countries, and we do not discount that important point. However, matching populations to markets does not currently drive the choice for research location.

REGULATION OF TODAY’S CLINICAL RESEARCH

We cannot stop clinical research from moving offshore, but we can characterize the factors that are pushing research offshore. In our paper, we discuss the administrative costs of clinical research in the United States. Systems developed to govern single-site studies are inefficient in the oversight of multicenter, multinational studies. Discussions about regulatory processes, such as institutional review board (IRB) processes, generally refer to early single-site studies, such as the Tuskegee and Willowbrook studies. In the aftermath of those studies, a regulatory infrastructure emerged that allows us to govern single-site studies. Today, however, clinical research is made up largely by multicenter, multinational studies.

The IRB processes can be incredibly redundant, especially at the site level. We cannot work as efficiently when we have 800 regulatory groups considering the same protocol. There also is redundancy in terms of contracting and the process with which academic institutions engage in this work. These and other barriers, such as intellectual property, add costs to the research process.

We also must address clinical research and compliance with the regulatory agencies; compliance has recently become a germane issue. Clinical research is potentially a criminal law issue; for example, if you incorrectly bill Medicare, you are liable from a criminal perspective, even for a simple accounting issue. As a result, not many people want to enter a career in which they are subject to criminal prosecution for recruiting patients to clinical trials.

A group of researchers at Vanderbilt University examined the process of undertaking federally funded cancer clinical trials. They found that, to establish a site in a National Institutes of Health (NIH)–sponsored clinical trial, the investigator must complete approximately 60 individual process steps. At a cancer center, the number of steps doubles to 110, and for a study with cooperative groups, the number of required process steps increases exponentially. The researchers considered how many of these steps could potentially add value to the research effort. They argue that less than half of the steps add any value. Investigators undertaking a new study may take up to 1000 days to complete approximately 60 individual process steps.
to start up a clinical trial, from the time of the initial concept, before they can begin to recruit participants to the study, which will then extend for another decade before the investigators answer their original question. This process is not efficient.

To obtain approval for a study, the investigator must first obtain signatures from members of the regulatory boards, such as the IRB. The number of signatures required adds to the process. For community practice sites, investigators may need to obtain as many as 12 signatures of approval. Investigators establishing sites at academic institutions will need almost 30 signatures, and for the core process within the cooperative groups, the investigator must collect more than 70 signatures. Each signature delays the investigator’s start time and adds complexity to the process.

In the movie Sicko, Michael Moore conducts a focus group in which participants discuss different health care systems. In thinking of this movie, I thought, “Our area has one of the largest growing Hispanic populations in the U.S. Wouldn’t it be interesting to sit down and ask Hispanic people in the local community, “Do you know what health insurance is? Would you actually be interested in health insurance?” To conduct an anonymous focus group, I would need to go through the IRB process to obtain approval to have 20 people in a room and to ask them, “What do you think about health insurance?” We began this process in August 2007: we submitted a protocol to the IRB and finally received IRB approval in January 2009. We are still working to begin the study.

This project is not funded, but in my situation, I can choose to pursue this study. However, if I were a resident, fellow, or trainee, and I wanted to pursue this—an interesting and relevant project that excites me and may drive my career—most people in this process would have sent me back to clinical work.

A few years ago, we considered the site-contracting process for clinical research. The contracting process for clinical research was almost twice as long at those institutions where they and the sponsors were negotiating contracts. Regarding that experience, Jeffrey Drazen wrote an editorial in the New England Journal of Medicine, stating that the regulatory system would be better served if regulating agencies used universally accepted contract language.

When we purchase homes, we sign contracts that take just minutes to sign. We cross out a line and add a line, and the contract process is complete. In contrast, a research institution will spend a year negotiating a contract with a sponsor to have 5 patients recruited to a clinical trial. Every time we negotiate this contract, the issues are identical, and 200 institutions in the United States will be conversing with the same sponsor about the same issues at the same time. The regulatory process is not adding value; the process is actually costing investigators time and money.

Regarding conflict of interest and the responsibility of investigators, the IRB at my institution now requires that I am familiar with all legal regulations regarding research. In fall 2008, the IRB added a 22-item contract in fine print in the institution’s electronic IRB form. I must sign this contract each time I submit a protocol. One item of this contract says, I’m familiar with and will comply with applicable federal regulations and guidance for protections of human subjects including all of these things from the Federal Register and associated guidance and Health Insurance Portability and Accountability Act privacy regulations, the Department of Health and Social Security, federal assurances, and relevant institutional policies and procedures for protection of human subjects.

I am not arguing that clinical investigators should not be responsible. I am concerned because I do not know where this massive information is accumulated for me to read and review, but I am responsible for all of this legal information. I met with the dean of research and explained to him that my research is almost all economics and outcomes work, and in fact, none of these regulations apply to my study. Regardless, if I want to conduct research, I must submit my protocol to the IRB, and when I submit my protocol, I must attest that I am accountable for all of these legal regulations. This process does not illustrate that the institution is trying to help me do clinical research.

CONCLUSIONS

In our paper about migration of clinical research abroad, we addressed a variety of issues, some of which relate to how we are pushing clinical research offshore and others to the regulatory oversight of clinical research that exists offshore. We discuss how to better train investigators in the United States, but we do not ask who is training investigators in India and China and who is tracking the data that foreign investigators submit to sponsors—the US Food and Drug Administration and the NIH. While the NIH is going through data to ensure that the investigators and the findings are credible, we do not have a database in which we enumerate investigators around the world who should not be conducting research.

More importantly, no one in the United States is responsible to advocate for clinical research. These regulatory groups that I mentioned are well intentioned—everyone is doing his or her best to address these issues—but no organization is responsible to unify these groups and say that we still want to do research in the United States.

We are all interested in pharmacogenomics. The United States spent a lot of money for the Human Genome Project, and I would like to see us use our findings here. A couple of weeks ago, I heard that a new therapy for Alzheimer disease was studied in China, and with the best genetic information we had at the onset of the study, investigators predicted that China would provide a great population for the study. Since the trial launched, however, US investigators found that the specific genotype is not prevalent in the Chinese population. Although we launched this therapy for Alzheimer disease in China, Chinese patients probably will not benefit because they do not have the relevant genotype.

Americans benefit from clinical research; however, we need to stop pushing this research offshore. We need to modernize the infrastructure for clinical research, and using the electronic health systems that physicians are beginning to use may help us modernize. At the same time, we need to modernize the administrative infrastructure for clinical research. We need to internally negotiate human-subject protection, contracting, and compliance and create a new standard that will protect patients and their interests but will also protect the explicit policy goal of conducting clinical research.