ESSAYS

The clinical research landscape is changing rapidly, and the system for overseeing research has failed to keep pace. The mechanisms for protecting subjects may be too stringent in some places, too weak in others, and overtaxed and unreliable overall. These essays survey the trouble spots and point the way to effective reform.

Trials and Tribulations

BY SUSAN GILBERT

By all accounts, Jolee Mohr was an active woman in relatively good health. Though she had rheumatoid arthritis, it did not keep her from holding down an office job and spending her leisure time boating with her husband and their young daughter. But the thirty-six-year-old Illinois woman's life came to an unexpected end last July, three weeks after an experimental gene therapy was injected into her right knee during a phase I/II clinical trial aimed only at assessing the agent's toxicity. Mohr's rheumatologist had recruited her for the study and had given her the injection in his office. Her death was caused by organ failure from histoplasmosis, a common fungal infection that normally produces only mild illness.

The tragedy immediately sparked comparisons with the story of Jesse Gelsinger, a vital eighteen-year-old who died in 1999 during a gene therapy trial at the University of Pennsylvania. Gelsinger's death was the first to be definitively linked to a gene therapy trial. Would Mohr's be another? The trial was halted pending an investigation by the National Institutes of Health's Recombinant Advisory Committee.

The RAC's report, released last December, delivered a mixed message. It concluded that the experimental treatment was unlikely to have contributed to Mohr's death, but it also said that the possibility "cannot definitively be ruled out." Howard Federman, the committee chairman, told *Science*, "we are still missing key pieces of information" needed to answer the ultimate question posed by Mohr's husband: Would she be alive today if she had not enrolled in the trial? In any case, the Food and Drug Administration allowed the trial to resume.

The investigation, though, brought to the surface disturbing aspects of clinical research left inadequately addressed since Gelsinger's death: the pressure to enroll record numbers of human subjects in record numbers of trials, financial conflicts of interest, shortcomings in oversight by the federal government and ethical review boards, and the implication of all of these trends for the safety of human subjects. These problems have been aired in medical and bioethics journals, op-ed pieces, and some memorable investigative journalism. But the Mohr case gave them new urgency. By infusing the all-too-familiar issues with flesh-and-blood drama, it revived concerns that clinical trials generally—not just research on gene therapy—may be headed for crisis.

So far, there are more questions than answers. Should someone who is not seriously ill be enrolled in a phase I safety study, or is the risk too high? What can be done to prevent subjects from developing the misconception that they will benefit from an experimental therapy? Is this misconception exacerbated when the researcher recruiting the subject is his or her physician? Did Mohr have this misconception, even though the consent form stated, "We do not expect you to receive any direct medical benefit from participation in this study"?

The financial relationships between drug company sponsors and researchers and between the drug companies and ethics review boards constitute a conversation all their own. What regulatory changes are needed to prevent financial interests from turning scientific research into a marketing tool and the ethical review process into a rubber stamp? Researchers are obliged to disclose any financial relationships with the research sponsor to the FDA, but not to potential research subjects. Would Mohr have consented had she known that her physician was being paid by the trial sponsor, Targeted Genetics, to

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recruit her for the study? Did the money lead her doctor, consciously or not, to talk up the benefits of volunteering for the trial and downplay the risks?

Government regulations are supposed to protect human research subjects from unethical treatment and unsafe conditions. But this task has gone from merely challenging to excruciatingly difficult in recent years. The explosive growth in the number of trials makes them harder to track. Changes in who conducts clinical research, and where, have shifted many trials into regulatory gray areas. And according to nearly all commentators, ethics review boards are strangled by red tape. All this leaves the courageous individuals who put themselves on the line in these trials more vulnerable than they are supposed to be.

Growth and Commercialization of Clinical Research

In the period from 2000 to 2006, the number of clinical trials in the United States jumped nearly 50 percent, from forty to fifty-nine thousand, according to CenterWatch, a company that tracks information on clinical studies. Along with this tremendous growth has come a significant shift in who finances and conducts trials. In 1991, 80 percent of them were funded by the federal government or philanthropic organizations and took place in academic medical centers. Now, most are financed by pharmaceutical companies and take place in private doctors' offices and clinics. A key driver of the clinical trials boom is the quest by drug companies for new blockbuster drugs to replace the ones that will go off patent in the next few years, including Lipitor for high cholesterol and Advair for asthma. With stiff competition and billions of dollars at stake, speed in testing new drugs is a high priority.

Frustrated by the slow pace of research at academic institutions, drug companies have turned to contract research organizations. These private companies, which manage trials and have a national and sometimes international reach, are better able than university medical centers to find the hundreds of thousands of researchers and millions of volunteers needed to keep clinical trials going year after year. They also complete trials faster, according to a 2006 study by the Tufts Center for the Study of Drug Development. CROs design protocols and frequently hire community doctors as investigators, often paying these doctors to recruit patients as study volunteers. CROs also cover the ethical review of clinical trials, hiring institutional review boards or even forming their own review boards. CROs were significantly involved in 64 percent of clinical trials in 2003, up from just 28 percent in 1993, according to CenterWatch.

The Tufts study found that the quality of the research was comparable in CROs and academic groups, but many experts are not so sure. In an article in the *New England Journal of Medicine* last October, Miriam Shuchman, a correspondent for the journal, explored questions about the qualifications of CROs, their ethics, their accountability, and their independence from their clients.

Many of the concerns can be traced to a groundbreaking investigation of CROs by the magazine *Bloomberg Markets* in 2005, which exposed some particularly egregious ethical and professional infractions at SFBC International, a large CRO. SFBC had put an unlicensed physician in charge of clinical trials in its Miami testing facility, the largest in North America, in 2005. The company targeted poor immigrants as human volunteers for the trials, enticing them with payments and neglecting to inform them clearly that participating in the trials carried risks of injury or death. The facility was shut down and last August the company, now called PharmaNet, settled a shareholder class-action lawsuit for $28.5 million.

The Mohr investigation highlighted some disturbing aspects of clinical research: the pressure to enroll subjects, the conflicts of interest, the shortcomings in oversight, and the implication of these trends for subjects' safety.

In Shuchman's view, one of the biggest obstacles to quality research by CROs is a workforce that has inadequate training and a high turnover rate. "CRO employees are generally younger, less skilled, less experienced, and less educated than researchers in the pharmaceutical industry or academia," she wrote, adding that staff turnover "can be as high as 100 percent during the lifespan of a single project."

Not surprisingly, the Association for Clinical Research Organizations, the trade group that represents CROs, rejects Shuchman's criticisms. "CROs draw their professional and research staff from the same pool of talent used by pharmaceutical and biotechnology companies," asserts the association's Web site.

Concern about inadequate training in clinical trials extends to private physicians, who make up a growing share of research investigators. In a survey of its membership in 2005, the American College of Physicians found that nearly 60 percent had been asked to participate in research in the previous two years, but that more than 33 percent felt unprepared to evaluate whether the research proposals were ethical. In re-

sponse, the ACP has developed an education program of resources and workshops on conducting office-based research. Educational information from the ACP discusses how to evaluate a study's validity, what constitutes fair compensation, and how to ensure proper ethical review. A document on its Web site called "Ethics Case Study" warns that ethical review under a CRO may not be sufficient, and it advises physicians to contract with a nearby academic IRB that may be willing to review protocols for a fee, which could then be billed to the CRO.

IRBs: Conflicts of Interest and Red Tape

One of the most heated debates about clinical trials concerns IRBs and how well they do their job. The federal government mandated the establishment of IRBs three decades ago to evaluate trial protocols, approve those that abide by a set of ethical principles, and monitor the trials to make sure that they uphold those principles. Regulations require IRBs to be without any conflicts of interest, but conflicts of interest are becoming harder to avoid.

When most research took place in academia, IRBs consisted of university researchers and clinicians who volunteered to review research proposals submitted by their colleagues. As the number of trials increased, academic IRBs became increasingly overburdened and overworked, and notoriously slow. For-profit IRB companies, promising greater speed and efficiency, came into being, and today, commercial IRBs review most clinical trials. Western IRB, the oldest for-profit IRB in this country, alone reviews more than half of all trials of new drugs submitted for FDA approval, including the trial in which Jolee Mohr participated. Several universities now outsource their research protocols to commercial IRBs.

Many ethicists and others involved with research policy deny that for-profit IRBs are capable of objective review. "Commercial IRBs have a fundamental conflict of interest," wrote Trudo Lemmens, an associate professor of law at the University of Toronto, and Carl Elliott, a professor of bioethics at the University of Minnesota, in *PloS Medicine* in July 2006. "They are in a client-provider business relationship with the commercial entities whose studies they review." Although the IRBs are subject to FDA regulations, the regulations "fail to prevent CROs from selecting the IRB least likely to reject the trial or delay approval by imposing too many restrictions," they wrote. "If one IRB is too stringent, they can simply go to the one next door."

The *Bloomberg* report described conflicts of interest between two commercial IRBs and the troubled companies whose studies they reviewed. Southern IRB was owned by the wife of a vice president at SFBC, the large CRO that employed an unlicensed physician and conducted inadequate informed consent. The Human Investigation Committee, another IRB, was founded by a doctor who ran the Fabre Research Clinic in Houston, a testing center that was closed in 2005 for falsifying records and numerous other legal and ethical violations.

An almost universal concern about federal regulations is that they add so many requirements for bureaucratic details that IRBs are left strangled by red tape.

Ezekiel J. Emanuel, chairman of clinical bioethics at the National Institutes of Health, disputes the criticism of for-profit IRBs. Although there have been no studies comparing their performance with that of academic IRBs, he points to two indicators of quality. For one thing, most of the unexpected deaths of relatively healthy research participants occurred in trials with academic IRBs (Jolee Mohr's was an exception). In addition, Emanuel said, the FDA has issued hundreds of warning letters to academic IRBs, but only one such letter to a for-profit IRB.

To be sure, conflicts of interest are not unique to for-profit IRBs. A survey of 574 academic IRB members revealed that a sizable minority have financial relationships that are relevant to their service on the IRB. The survey, published in the *New England Journal of Medicine* in 2006, found that 15 percent of the IRB members had conflicts of interest, meaning that they reviewed at least one protocol sponsored either by a company with which they had a relationship or by a competitor of that company. Nearly one-quarter of the IRB members with conflicts of interest said that they never disclosed them to their IRBs. The process for disclosing conflicts of interest was unclear to many of the respondents, with 33 percent saying either that their IRB had no formal disclosure process or that they did not know of one.

Conflicts of interest need not be financial. Most members of IRBs at medical schools are employees of those institutions and have personal relationships with the researchers. These ties may make it difficult for academic IRBs to be objective in evaluating their institutions' protocols. "Disapproval of such protocols means that less money will flow into the institution and its clinical-trials operation, with a potential deleterious financial effect," wrote Franklin G. Miller of the National Institutes of Health last March in a letter in the *New England*

Journal of Medicine. Paul Gelsinger, Jesse's father, raises the possibility of conflict of interest at the University of Pennsylvania IRB that reviewed the trial in which his son died. Most of the IRB members were university employees.

No one knows how often conflicts of interest lead IRBs to approve clinical trials of questionable ethics or scientific value. Research on that question would be a giant step toward improving ethical reviews, but would likely not be sufficient to ensure that IRBs can do their jobs. Experts point to another major problem plaguing IRBs: regulatory bureaucracy.

An almost universal concern about federal regulations is that they have left IRBs strangled by red tape. In the name of human research protection, regulations have added so many requirements for documentation and other bureaucratic details that IRBs appear at times to have lost the forest for the trees. "The national system for the protection of human research participation is indeed a system in jeopardy," asserted Norman Fost, director of the program in medical ethics at the University of Wisconsin, and Robert Levine, a clinical professor at Yale, in a widely read editorial in the *Journal of the American Medical Association* last November. Fost and Levine criticized the regulations for "meticulous documentation of compliance with narrow interpretations of regulations and policies." And they warned, "In some cases, these activities actually appear to be reducing protections for participants in research." (This opinion is echoed by Greg Koski, the first director of the Office for Human Research Protections, in an essay in this issue.)

In a wrongful death lawsuit, Paul Gelsinger charged the University of Pennsylvania IRB with inadequate oversight caused not only by conflict of interest, but also by an excessive workload. The lawsuit was settled out of court, leaving the IRB's responsibility for Jesse's death unresolved. What role, if any, IRBs have played in the handful of other unexpected deaths in clinical trials is unclear. But Fost and Levine believe that the increasing bureaucratic burden being placed on IRBs would not have prevented any of the deaths. "To the contrary," they wrote, "the increasing focus on minutiae has been distracting IRBs from more substantive issues." Those issues include a lack of clarity in the informed consent process.

Commentators who want to restore IRBs to their mission of protecting human research subjects are now calling for change from everyone involved in clinical trials—the FDA, OHRP, research institutions, and scientists themselves. Koski lays some of the blame for the increased red tape on scientists who try to skirt regulatory oversight by passing off their clinical research as quality improvement projects, which are exempt from IRB approval. Were researchers to act more responsibly, he argues in his essay, regulations could be relaxed and IRBs could be more flexible. Koski suggests that OHRP work with the research community on this shared goal.

Regulatory Oversight: Overburdened and Outdated

Recent research points to other problems with the regulatory system. Last September a report showed that the FDA audits fewer than 1 percent of all sites where new drugs and medical devices are tested. The report, by the Inspector General of the Department of Health and Human Services, found that the agency was simply overwhelmed.

Still another problem is that the regulatory system is outdated. The regulations were written in the 1970s, decades before CROs even existed. CROs constitute a regulatory gray area. It is not clear who is responsible for reporting adverse events to the FDA: the drug company sponsor of a trial or the CRO that the company hires. Such confusion can cause adverse events to go unreported.

In her *New England Journal of Medicine* article, Shuchman described how hazardous side effects nearly fell through the cracks in a postmarketing safety study involving aprotinin (Trasylol), an antifibrinolytic drug made by Bayer. Researchers with Ingenix, the CRO hired to conduct the study, found that people who took the drug were at increased risk of kidney failure, heart failure, stroke, and death. The CRO reported these problems to Bayer, but Bayer did not report them to the FDA. It was only after Alexander Walker, a re-

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Microscope, by Tom Otterness, 2007, edition of 9, 17.5"x9"x3.5," photo by Jean Vong. Courtesy of the artist.

searcher with the CRO, said that he would contact the FDA himself that the drug company reported the adverse events.

It's harder for the FDA to find out about adverse events and violations in privately funded studies than in publicly funded ones. "If the research is privately funded, there's less federal oversight," said Michelle Mello, an associate professor of health policy and law at the Harvard School of Public Health. "Federal funding is a hook that the government can use for oversight. When there isn't funding involved, the government has to work a little harder."

It must work harder still when clinical trials are conducted abroad. A new trend is to move clinical trials to India, China, and Eastern Europe. In 2007, 38 percent of trials registered on ClinicalTrials.gov were conducted overseas, up from 16 percent in 2001. Pharmaceutical companies expect that up to 65 percent of their FDA-regulated clinical trials will take place offshore within the next two to three years, according to the Tufts Center for the Study of Drug Development.

"It's easier and cheaper to recruit subjects in India and Eastern Europe," said Mello. But, she said, there is less protection for research subjects; federal regulations do not extend to all American-based trials conducted abroad. And yet these subjects are particularly vulnerable to exploitation because of low education levels, illiteracy, language barriers, and poverty. "Aside from formal regulatory structures, there's the question of what's going on at research sites abroad," she said. "In many developing countries, the infrastructure for human subjects protection isn't what it is here." The Tufts Center predicts that over the next several years, drug sponsors, regulatory agencies, and human subjects protection programs will increase training and oversight of foreign-based investigators to bring them into compliance with U.S. regulations.

Toward Safer Trials

The conversations about regulatory failures, conflicts of interest, and other threats to clinical research are beginning to yield plans for averting a crisis. Responding to doubts about how well Jolee Mohr understood the risks of the Targeted Genetics trial, the American Society of Gene Therapy is looking for ways to clarify the informed consent process. "Informed consent is challenging," said Arthur W. Nienhuis, president of the gene therapy society. "There's always concern about therapeutic misconception, especially when clinical investigators are often physicians recruiting their patients."

The American College of Physicians' educational program appears to be helping to improve communication between physician-researchers and the patients they recruit for clinical trials. The ACP has a brochure for doctors to hand out to patients who are considering participating in clinical trials. It includes a long list of questions for patients to ask, such as: What are the potential benefits and risks to me of participating in the study? Who is paying for the study? Who will make money from the results? As both a researcher and my doctor, how will your research goals affect your decisions about my regular care? "From what we have heard from physicians, we think the program has been of assistance in raising consciousness about research integrity and ethics issues," said Lois Snyder, director of the ACP's Center for Ethics and Professionalism.

Another sign of hope came last September, when the Food and Drug Administration Revitalization Act was passed. It contains a new requirement that efficacy trials be registered in a national database, and that all findings be available for anyone to read. This stipulation should make it harder for drug companies to hide adverse events. The act also increased the FDA's funding, which, with any luck, will translate into more inspections of clinical trials.

Where to begin reforming the oversight of clinical trials is more challenging and controversial. How can the regulatory reins on human research be eased to lessen the bureaucratic stranglehold without sacrificing bedrock protections of clinical trial subjects? What should be done to minimize conflicts of interest in clinical research and on ethical review boards? What would it take to change the culture of clinical research to make all the participants—researchers, IRBs, and regulatory agencies—more committed to protecting human volunteers? There are no answers yet. But at least the questions are being asked.