Trials with Errors — Preserving the Integrity of Clinical Trials

by Ruth Levy Guyer

The crucial final test of medical research is the clinical trial, which determines whether a drug or discovery really is an effective therapy. All people who participate in clinical trials — researchers, sponsors, volunteers, analysts, reviewers, overseers, others — have opportunities to strengthen or weaken the integrity of the trial system by their behavior.

Medical research is now officially married to business, and "profitable" connotes something different to each partner. Only if research and business can profit in parallel will the alliance succeed. Every person who is involved in the medical research business faces temptations and must choose how to react. Each has power and must choose how to wield it. Several centuries before this marriage, the Englishman Izaak Walton noted that "Health is . . . a blessing that money cannot buy."

Clinical trials are the hoops that pills, vaccines, and other new therapies must jump through before they can be approved for use in the United States. Trials establish — or don't — that a new treatment works, that it is safe, and that it is better than or as good as all other existing therapies for the condition or disease under study.

Built into the trial process are a number of checks and safeguards that, when strictly observed, assure the credibility of the results. An oversight committee, called an institutional review board (IRB), examines each experiment to determine that its design is solid and that participants will not face excessive risks. People who are considering participating in a trial — labeled "volunteers" — learn what they will be getting into through an informed consent document that spells out the purpose and shape of the experiment, its potential benefits and risks, the rights and responsibilities of volunteers, and the objectives and obligations of researchers. At the trial's end, examiners at the Food and Drug Administration (FDA) review the data before okaying the pill or treatment for sale in the marketplace.

Then and Now

During the many decades when medical research in the United States was a fervid but somewhat sleepy enterprise funded mostly by the federal government, the results of clinical trials interested researchers, volunteers, and those whose lives might be improved by a new treatment. All shared a hope that the drug or therapy under study would cure or at least ameliorate the target medical problem.

Today, medical research is a scaled-up, megabuck, big big business, hurtling along a fast industrial track. Trial results still captivate researchers, volunteers, those suffering from target diseases, and those providing oversight (IRB) and approval (FDA). In addition, the pharmaceutical and biotechnology companies that make drugs and run trials watch clinical trials closely, as do the companies' investors, print and broadcast journalists, and editors and readers of the scientific and medical literature.

In an ideal world, these onlookers all would be eager to learn about the achievements and promises of the treatments under study. In the real world,

many do care about theraputic applications and implications. But some only care that new therapies benefit them financially. And a disturbing subset of these hope simply to make a quick buck — caring not whether the treatment is genuinely effective but only that, in the short term, it give the appearance of being a success.

With speed and money serving today as engines driving a large fraction of medical research — companies now fund 70 percent of all clinical trials of drugs in the United States (Bodenheimer 2000) — opportunities have burgeoned for researchers and trial sponsors to make and overlook errors, rig trials, and commit fraud.

The clinical trial system, although in jeopardy, is certainly not rotten to the core. Many trials still run smoothly, are not compromised by conflicts of interest, and achieve the central aim of medical research — the development of treatments, palliations, and cures. But medical research requires money. And, although businesses are game to spend that money, they will do it only if they can fulfill *their* central aim — making more money. These disparate goals must now be met concurrently, if new, effective therapies are to be staples of the future.

How can the integrity of the clinical trial system be maintained in this high-pressure, tantalizing environment? As with other global problems, the solutions begin locally — at each trial, with each player. Awareness is the first step, both of what clinical trials achieve and what could be lost forever if the trial system is allowed to slip into degeneracy. Action is next, requiring a conscious commitment to responsible behavior on the part of all participants — volunteers, researchers, companies and other sponsors, investors, overseers, policymakers.

In the end, drugs and treatments that don't work help no one live a healthier life. Even the most ardent investors and business executives have concluded, when facing their own mortality, that medical research goals must supersede business goals.

The Power of Volunteers

No one may be able to exert more muscle toward keeping clinical trials focused on medical goals than volunteers. Computer simulations, experiments with animals, and studies in test tubes go only so far toward shaping new therapies. Eventually all drugs and treatments must be tested in people.

Trial volunteers lend their bodies to medical research. They have the right to know how their bodies will be used. And they have the right to refuse to volunteer. The crucial guiding principle of voluntariness is consent that is informed, not coerced.

Volunteers have a right to have all their questions answered; they should also consider that becoming fully informed is their solemn responsibility.

Some ten to nineteen million volunteers participated in trials in the United States in the year 2000 (Shamoo 2000). Each had to sign an informed consent document. Few researchers actually test volunteers to make certain they understood what they read, so truly "informed" consent is hard to prove. But volunteers in such staggeringly large numbers could wield tremendous power over the conduct of trials simply by refusing to sign forms that are murky or rife with medical and legal jargon that is intelligible only to medical scientists and not even to the much-spoken-of rocket scientists. Volunteers have a right to have all their questions answered; they should also consider that becoming fully informed is their solemn responsibility.

In reality, many volunteers join trials for reasons that are quite independent of understanding absolutely their benefit-to-risk ratios. Some patients enter trials as last-ditch efforts to achieve relief from suffering. Their hopefulness, a powerful factor in illness and recovery, may not be subject to alter-

Checklist for Volunteers

Get informed before you volunteer. The consent form or the researcher should answer these questions. If all else fails, call the IRB.

- ❑ What is the purpose of the study? What are the risks? Might there be benefits?
- ❑ What is the phase of the trial: safety testing, efficacy testing, or comparison of drugs?
- ❑ Are the drugs approved (known to be effective) or investigational or experimental (just being tested)?
- ❑ Is this pure research or does the trial include therapies?
- ❑ If this trial includes therapies, is one option a placebo?
- ❑ Who is the appropriate volunteer? Do I fit this profile?
- ❑ What is the reputation of the researcher? What ties does the researcher have to the sponsor?
- ❑ Who is getting paid for my participation: me, the researchers, others?
- ❑ If something goes wrong, who will treat me? Who will pay for my medical care?
- ❑ Who will have access to the data and my medical records? Where are these data stored? How secure are they? Can the researchers or others use these data in future studies that are unrelated to this study?
- ❑ Who is sponsoring the trial: the federal government, a pharmaceutical or biotechnology company, a medical center, someone else?
- ❑ Is there a chance that the trial will be stopped early if the test material is effective? Would I then receive the test material no matter what group I started in?
- ❑ Who do I contact with questions and concerns?

ation by analytical information. Some patients — from gravely ill to just diagnosed — know that a given trial will not help them personally, but they sign on in order to help others down the road who have the same disease. For many with diseases that are encoded in the genes, the impulse to help others may not be broadly altruistic but directed toward helping their own children and other affected relatives. Some patients join trials because a trusted doctor is in charge, and they wish to reciprocate for the care they have received by supporting the doctor's initiatives.

Motivations of healthy volunteers also can range widely. Some are altruistic. Others are interested generally in advancing medical science. Still others want to make money. Some people actually make a living going from trial to trial, although *biopimping* (Lemmens and Elliott 1999), as it is inelegantly called, is not exactly a get-rich-quick scheme.

Remuneration may be fitting compensation for those who take personal risks and contribute time to trials. But medical ethicists and others worry that the practice of paying trial participants can never be fully compatible with the spirit of volunteerism, which includes some form of personal sacrifice — time, energy, discomfort, and risk. The lure of money clearly can cloud judgments, and it may leave only the most vulnerable people — the poorest, those with the least ability to under-

stand — in the position of "volunteering" for the highest risk trials. Justice thus is an issue here: the dictum "first do no harm" applies equally to treatment of the weak, the strong, and the powerful, but only the latter two may have the luxury of turning down cash payments.

Volunteers always have the option of leaving trials. If a volunteer is uncomfortable, sees improprieties, or has other concerns, and, if conversations with the researcher do not lead to an accommodation, then it is time to bail out. Volunteers have also sabotaged experiments that they sensed were unfair and coercive. In the 1950s and 1960s, for example, prisoners at Pennsylvania's Holmesburg Prison felt objectified by a dermatologist who described them as "acres of skin." The researcher plastered each man's back and arms with gauze patches soaked with radioactive materials, LSD, and other potentially dangerous compounds and, days later, observed and recorded the effects. But some prisoners took off their patches the moment they returned to their cells and slipped them back right before the assessment. "Those doctors were running a game on us," said one prisoner, "so we ran a game on them (Hornblum 1998)."

In another experiment, an early test of the AIDS drug AZT, patient volunteers were angry to learn that half of the group would receive the new test drug and half would only receive placebos (Toynbee 1996). They secretly pooled and shared all their pills so that everyone got some AZT. In this trial, the volunteers did not understand that a fundamental of experimentation is that every experiment includes controls, that not all trials deliver therapies, and that not every test drug is better than no therapy at all. (A well-known phenomenon, called the placebo effect, indicates that about a third of the time placebos — blank pills — work as well as specific therapies.) AZT turned out to be much better than a placebo, but this trial did not contribute to that proof.

Most clinical trials are not standoffs between volunteers and researchers. They are joint ventures that succeed when the players share a purpose, information, and even control.

Phases of Clinical Trials

Phase I trials examine whether a drug is safe for human consumption or toxic. Healthy volunteers ingest the drug or receive an injection. Researchers assess the drug's absorption, metabolism, excretion, and side effects.

Phase II trials assess whether a drug works and how it compares to controls and placebos. These trials may have therapeutic effects and thus generally involve volunteers with the target disease or condition.

Phase III trials scale up the phase II test to hundreds or thousands of people.

Phase IV trials compare the drug with existing drugs already on the market. These trials last longer and provide information about a drug's long-term efficacy.

Responsibilities of Researchers

The early medical researcher had the skills and interests of both a scientist and a doctor. After conceiving of a new drug — following years of painstaking work or, on occasion, in a single "eureka" moment — the researcher prepared the drug, tested it in the laboratory, and then enlisted human volunteers to help establish that the drug was not toxic, was effective, and worked better than other existing therapies. Some over-zealous researchers needed reminders as they moved from laboratory to clinic that their foremost obligation was to the safety of the volunteers rather than to research goals, and that is one role that IRBs assume.

Today, only the rare researcher would still shepherd a new drug from concept to caplet. More often, the lengthy process (typically, seven to twenty years) involves people who design drugs, and those who design trials, recruit volunteers, conduct trials, analyze and report results, and so on. Large multisite trials pull in even more players, enlisting the help of doctors throughout the country or around the world to find suitable volunteers in their communities.

The metamorphosis of the medical researcher into a conglomerate has weakened some important provisions of the clinical trial system. Most worrisome are lapses in safeguards for ensuring the ethical treatment of volunteers. If each member of the conglomerate feels like a small cog in a large wheel, no one may be entirely clear who bears responsibility for the volunteers' safety (Moreno 2000). Each may think the ethics buck stops elsewhere. In that uncertain environment, the ethics buck may fall straight through the cracks.

Requirements to disclose conflicts are helpful but may meet only the letter and not the spirit of objectivity, an absolutely crucial characteristic for researchers and others who conduct clinical trials.

The other buck imperiling the clinical trial system is green, and its influences are wide ranging. Financial entanglements between doctors and companies begin the moment a company representative hands a freshly minted doctor a long-coveted, monogrammed, black medical bag. Thereafter, free samples of drugs, fancy meals, paid speaking engagements, prized seats at concerts and sports events, and other gifts subtly, or not, draw the doctor's allegiance toward the company.

Today, many doctors are paid handsomely by companies to help with clinical trials. Usually the payments are on a per-volunteer basis, and they go far to shore up the incomes of doctors hit hard by managed care. Doctor-researchers may so desperately want a test drug to succeed — to please the sponsors, to receive promised payments, to protect their own investments — that they fail to report side effects, ignore signs that the drug is not working, and even enroll unqualified volunteers just to meet their quotas.

The involvement of tens or hundreds of people in each clinical trial means that, long before the data are carefully reviewed and published, many people become aware of promising and disappointing results. In 1997, the Securities and Exchange Commission filed its first insider trading case against a biomedical researcher who, seeing that a test drug was a dud, leaked the news to friends who had invested in the drug's manufacturer (Ferguson 1997).

Financial conflicts of interest are growing. Requirements to disclose conflicts are helpful but may meet only the letter and not the spirit of objectivity, an absolutely crucial characteristic for researchers and others who conduct clinical trials.

Pre-Trial Review by Institutional Review Boards

IRBs approve all experiments that will be conducted with human subjects. They examine the plan for the trial — called a protocol — and the consent document. They can approve these as written, block them, or require researchers to make specific changes. IRBs include a mix of individuals — people from the medical, research, and local lay communities, medical ethicists, clergy, lawyers, and others — whose distinctive perspectives all help ensure that the trial will be fair to volunteers and will achieve important medical objectives. All studies paid for by the federal government or carried out at institutions that receive federal funds must be approved by an IRB. Companies also pass their experiments through IRBs, which gives them important legal protections.

IRBs have always grappled with potential biases and lapses. When most IRBs were housed at institutions that reviewed trials proposed by local researchers, members of the IRB sometimes seemed too eager to rubberstamp those submitted by their close colleagues — "old boy" and, less often, "old girl" courtesies. In addition, on occasion, members of an IRB lacked the necessary expertise for a thorough review but approved a trial anyway, especially when they were swamped with work.

Today, IRBs face additional potential conflicts. Profitmaking, private, independent IRBs find that,

to stay afloat, they must balance their criticisms with enough approvals to keep researchers interested in submitting protocols to them (Veatch 2000). And the IRBs that are convened by and work for just one company include some members who are not entirely comfortable challenging trials proposed by those who pay their salaries.

IRBs were established to safeguard volunteers (<www.nih.gov/grants/oprr/humansubjects/45cfr46.htm>). This is still their primary charge and one that members must accept wholeheartedly, irrespective of their personal relations and financial links.

Post-Trial Review by the Food and Drug Administration

Investigators at the FDA give their stamp of approval only to drugs that pass stringent safety and efficacy trials. As a result, many fewer approved drugs get withdrawn from the shelves here than in other countries, including France, Germany, and Britain (Wolfe 1996).

The FDA has hired hundreds of new investigators in the past decade to help process the many new drugs and treatments that companies are trying to market. A survey in 1999 indicated that more than half of these investigators had financial ties with pharmaceutical companies that were seeking FDA approval for some product (DeAngelis 2000). Recusal is crucial in such situations, because the professional responsibility of the FDA investigator is to protect consumer safety, not personal investments.

Headline Medicine

Most medical advances are incremental. They are not earthshaking. But for a medical story (or any story) to hit the front page or garner airspace, it must have a flashy news hook. Many journalists skillfully balance facts, investigation, skepticism, and reporting. Others do not. In trying to dazzle readers, satisfy editors and publishers, and promote certain researchers or products or therapies, some journalists stretch or lose sight of the truth. Several years ago, one journalist was caught hyping a medical story that was about to land her a lucrative book deal (Cimons 1998).

A good day for a mouse does not always presage a cure for a human disease. Nor does a change in blood chemistry mean that a health problem has been solved. Truly newsworthy clinical trials are those that make volunteers feel better. Medical news that is reported in the business section of a newspaper — an increasingly common phenomenon — is probably meeting more business goals than goals of research.

Medical and Scientific Journals and Other Resources

Medical advances have always been published in professional journals after thorough vetting by the researchers' peers. Publication gives others a chance to assess raw data and repeat and confirm experiments. "Work that remains unpublished," wrote one researcher in 1994, "is essentially incomplete or undone (Rangachari 1994)." Rarely, but occasionally, when an urgent public health issue is at stake, responsible editors will allow researchers to tell their stories to the media before the journal's publication date (Fontanarosa 2000, 2929).

When a study is considered particularly significant, a journal sometimes runs an editorial or review along with the report to help readers understand the study's importance. Recently one prestigious medical journal apologized for printing commentaries by researchers who had financial ties to trial sponsors (Angell 2000). Commentaries written by biased authors obviously lack all credibility.

Listings of Clinical Trials on the Internet

Federal — http://clinicaltrials.gov/

Industry — http://www.centerwatch.com/

Others — Use any search engine and search for "clinical trials."

Currently some 500,000 articles are published each year in medical and scientific journals (López-Jiménez 2000). Most report good news. (Researchers rarely publish totally negative results.) How trustworthy is the data? One survey in 1997 indicated that, of 100 studies of new drugs, every single one concluded that the drug of the study's sponsor was more effective than control drugs (Rule and Shamoo 1997). If readers are to believe what is published, journal editors and reviewers must start reading more closely than ever and between the lines.

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Researchers no longer have exclusive ownership over medical information. Anyone with a computer can tap into that mammoth database of medical literature called Medline, which now receives more than a million hits a day (<http://www.nlm.nih.gov/databases/freemedl.html>). Many journals are already online; others are heading there. The web is a useful resource, replete with facts about diseases, drugs, treatments, and trials. Unfortunately, it is also loaded with factoids and fantasies, wild claims, and pseudoscience. On the web and in other medical resources, information and misinformation sometimes look much alike. Caveat emptor.

On the Horizon

The research enterprise of the twentieth century was as successful as it was because clinical trials were carefully constructed and monitored, and data from them could be trusted. Will clinical trials survive the merger of medical research with big business?

Let's hope so. Trials are important. Without them, the medical future would be exactly like the present. No new treatments would become available, and the great potentials of molecular medicine, genomic analysis, and nanotechnologies for improving the human condition would go unrealized.

Yet, even if the clinical trial system becomes rock solid ethically and scientifically, medicine, being both science and art, will remain an iffy enterprise. Individuals' personal "experiments" with proven therapies will always continue long after trials end. A bottle label may declare that 99.8 percent of the time, a pill produces a certain result, say, tames a headache. But 99.8 percent is only a statistic; it tells what will happen to groups of people, not specific individuals. Individuals, with their idiosyncratic, genetically determined susceptibilities, have different innate capacities to perceive and respond both to the pain of the headache and to the salutary effects of the pill. As long as the pill's effectiveness is only 99.8 percent, some luckless individuals must be in the outlier 0.2 percent group. Their plights are to go on aching, pill or no pill, reputable clinical trial or not.

References

Angell, Marcia, Robert D. Utiger, and Alastair J.J. Wood. 2000. "Disclosure of Authors' Conflicts of Interest: A Follow-Up." *NEJM* 342(8): 586-587.

Bodenheimer, Thomas. 2000. "Uneasy Alliance: Clinical Investigators and the Pharmaceutical Industry." *NEJM* 342(20): 1539-1544.

Cimons, Marlene, Josh Getlin, and Thomas H. Maugh. 1998 "Cancer Drugs Face Long Road from Mice to Men." *Los Angeles Times*, May 6, A1.

DeAngelis, Catherine D. 2000. "Conflict of Interest and the Public Trust." *JAMA* 284(17): 2237-2238.

Ferguson, James R. 1997. "Biomedical Research and Insider Trading." *NEJM* 337(9): 631-634.

Fontanarosa, Phil B., A. Flanagin, and Catherine D. DeAngelis. 2000. "The Journal's Policy Regarding Release of Information to the Public." *JAMA* 284(22): 2929-2931.

Hornblum, Allen M. 1998. *Acres of Skin*. New York: Routledge.

Lemmens, Trudo, and Carl Elliott. 1999. "Guinea Pigs on the Payroll: The Ethics of Paying Research Subjects." *Accountability in Research* 7:3-20.

López-Jiménez, Francisco, et al. 2000. "Update in Internal Medicine." *Archives of Medical Research* 31: 329-352.
Moreno, Jonathan D. 2000, personal communication.
Rangachari, R.K. 1994, "The Word Is the Deed." *Advances in Physiology Education* (December): S120-136.
Rule, James T., and Adil Shamoo. 1997. "Ethical Issues in Research Relationships between Universities and Industry." *Accountability in Research* 5:239-249.
Shamoo, Adil, 2000. "The Business of Human Experiments."Estimate given at the Third National Ethics Conference at the Friends Research Institute, Inc., Baltimore, MD. (November 3-5).
Toynbee, Polly. 1996. "No One Really Wins." *The Independent* (London), May 29.
Veatch, Robert M. 2000, personal communication.
Wolfe, Sidney M. 1996. "Save the Gold Standard in Public Health." *Tampa Tribune*, July 29, 9.