

SELECTED SUMMARY

Should trial subjects be unionised?

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Elliott C. GUINEA-PIGGING: Healthy human subjects for drug-safety trials are in demand. But is it a living? *The New Yorker*. January 7, 2008

As recently as 1991, 80 per cent of industry-sponsored drug trials in the United States were conducted in university hospitals. Today, with pressures to bring drugs to market quickly, more than 70 per cent of the trials are conducted in private "contract research organisations" (CROs) to accelerate every phase of drug development. "Volunteering" for clinical trials has become a new occupation. The best-paying studies are longer, in-patient trials that may involve invasive procedures. The subjects are usually unemployed, college students, contract workers, ex-cons, or young people who require money. This has produced a community of "guinea-pigging" semi-professional research subjects, who enrol in one study after another. Most are involved in Phase I trials and cannot expect any benefit in return for the risks. "... their reason for taking the drugs is no different from that of the clinical investigators who administer them, and who are compensated handsomely ... This raises an ethical question: what happens when both parties involved in a trial see the enterprise primarily as a way of making money?"

In May of 2006, Miami-Dade County, in the US state of Florida, citing fire and safety violations, ordered the demolition of the largest drug-testing site in North America, a former 675 bed motel in a downtrodden neighbourhood. The operation had closed down after *Bloomberg Markets* reported that SFBC International, the owner, was paying undocumented immigrants to participate in ethically dubious drug trials often approved by a commercial ethics review board owned by the wife of an SFBC vice-president. In 1996, the *Wall Street Journal* reported that the company Eli Lilly was using homeless alcoholics to test experimental drugs at budget rates in Indianapolis, in the US state of Indiana.

American system of supervision of clinical research

In the 1970s, the United States Food and Drug Administration was empowered to monitor research involving human subjects. The FDA requires that all studies be approved by an institutional review board (IRB). The rules were drawn up when all studies were conducted in universities where faculty members volunteered to serve on a review board to evaluate studies by their colleagues. With the establishment of for-profit CROs, review and supervision of clinical studies has now shifted to commercial IRBs. These for-profit IRBs compete for clients by promising a fast review. And if one for-profit IRB concludes that

a study is unethical the sponsor can simply take it to another. Moreover, because IRBs scrutinise studies only on paper the violations of SFBC in Miami would not be covered in the IRB review. "FDA inspections focus more on verifying clinical trial data rather than human-subject protections." It was only in 2005 that FDA inspectors were authorised to report on the safety and welfare of the research subjects.

As a result, guinea pigs rely on their wits or word-of-mouth to determine which studies are safe. Some develop a relationship with recruiters they trust. "In general, guinea pigs figure that sponsors have a financial incentive to keep them healthy ... but companies also have an interest in things going well as cheaply as possible, and this can lead to hazardous tradeoffs." Indeed, in March 2006, in a phase 1 trial of a monoclonal antibody in a hospital near London, six volunteers required hospitalisation in a critical care unit and all have been left with disabilities. A previously healthy 19-year-old student committed suicide in a safety study of Eli Lilly's antidepressant Cymbalta in January 2004. An Iraqi immigrant in Canada, in need of an income, enrolled in an immunosuppressant trial at a Montreal-based subsidiary of SFBC. He was given a bed next to a subject who was coughing up blood. Despite his complaints, he was not moved to a different bed for nine days. He and eight other subjects later tested positive for tuberculosis.

In the 1990s, Abuzzahab, a psychiatrist, had his license suspended and was ordered to take a class in medical ethics. Abuzzahab had "enrolled psychiatrically disturbed and vulnerable patients into investigational drug studies without ensuring that they met eligibility criteria and then kept them in the study after their conditions deteriorated." One case involved a 41-year-old schizophrenic woman who was doing well on her medications until Abuzzahab switched her to an experimental agent. She became suicidal and yet was allowed to leave the hospital on a day pass. She threw herself in the Mississippi river and drowned. In another case, Abuzzahab had prescribed a "large supply of potentially lethal medications" to a suicidal woman with a history of substance abuse. She committed suicide by taking an overdose.

The lawsuits and public disciplinary action by the state licensing board seem to have had no effect. Abuzzahab continued to supervise drug trials, and to receive payments from at least a dozen drug companies. Strangely, in 2003, the American Psychiatric Association awarded him a Distinguished Life Fellowship.

The US regulatory system is designed to check excesses by academics in search of medical knowledge or academic advancement by ensuring that studies are subject to peer review. CROs' research is seldom published in academic journals. Pharmaceutical companies often pay a \$30,000 bonus, plus \$12,000 for each subject enrolled and an additional \$6,000 for each subject beyond the first six subjects. Some of the people conducting clinical trials have little training in how to conduct research. And, as the Abuzzahab case suggests, not all drug companies are especially selective about the researchers they hire. In 2001, the FDA asked the pharmaceutical company Sanofi-Aventis to perform new studies of the antibiotic Ketek, which was suspected of causing liver failure. Reports later revealed that the top-recruiting investigator hired by PPD, the firm contracted to conduct the studies, was a graduate of an offshore medical school who tested the antibiotic on clients in an obesity clinic she ran in Alabama. Another top recruiting investigator was arrested when the police found him carrying a loaded semiautomatic handgun, and hiding cocaine in his underwear.

In 1996, Helms, a guinea pig and former union organiser, started a jobzine for research subjects called *Guinea Pig Zero* which publishes how well a study paid, the competence of the venipuncturist, the quality of the food, and a report card grading research units from A to F. It is aimed at poor people who sign up for studies in order to earn a livelihood.

Guinea Pig Zero assumes that subjects should get more money, while many ethicists and regulators argue that they should get none at all. The standard worry expressed by ethicists is that money tempts subjects to take part in dangerous, painful, or degrading studies against their better judgment. FDA guidelines instruct review boards to make sure that payment is not "coercive" and does not exert an "undue influence" on subjects. Ethicists prefer that subjects take part in studies for altruistic reasons. If altruism was the only reason, phase 1 studies would find no subjects. IRBs allow sponsors to pay guinea pigs, but, consistent with FDA guidelines, insist on their keeping the amount low. Sponsors refer to the money as "compensation" rather than as wages, ... but guinea pigs must pay taxes, receive no retirement benefits, disability insurance, workmen's compensation, or overtime pay." Most do not have any health insurance and often cannot pay for their care if they are injured in a study -- only 16 per cent of US academic medical centres provided free care to subjects injured in trials.

Guinea pig activists recognise that they are indispensable to the pharmaceutical industry; a guinea pig walkout in the middle of a trial could wreak financial havoc on the sponsor. Yet the conditions of guinea-pigging make any exercise of power difficult. Not only are those in a particular trial likely to be strangers; if they complain to the sponsor about conditions, they risk being excluded from future studies. And, according to *Bloomberg*, when illegal immigrant guinea pigs at SFBC talked to the press, managers threatened to have them deported. Lawsuits on behalf of injured subjects are growing, and research sponsors as well as the IRBs are the targets.

"The safety of new drugs has always depended on the willingness of someone to test them, and ... the job will fall to people who have no better options. Guinea-pigging requires no training or skill, and in a thoroughly commercial environment, where there can be no pretense of humanitarian motivation ..."

Discussion

In the aftermath of the Tuskegee experiments, the US congress enacted laws that required the FDA to assure that an independent IRB review the study design for adherence to ethical norms including adequacy of protection for the subjects, a consent form that reasonably informs the research subject of her/his options as well as for scientific validity of the research. US universities by and large adhered to these standards. Thus, an elaborate system for review of all human experimentation exists at all academic centres. The process is deliberative, involved and often appears excessively bureaucratic. With the marked increase in new drug development, it is not surprising that the industry would seek another source for drug testing.

In academic circles, drug studies do not have the same value as bench research. You take up a pharmaceutical study for the income it will bring in to the department or institution to support other research projects. The doctors conducting the studies get no additional income from participating in the research. Thus, for the academician, there are neither significant academic gains nor monetary gains from participating in clinical drug testing. This limits the number of clinical pharmaceutical studies; particularly phase I trials, that the universities are willing to do. The academicians may be more inclined to carry out phase III studies when a drug appears particularly interesting, as the possibility of publications may enhance their academic standing. Also, while the reimbursement from the sponsoring corporation may not directly enrich the researcher, the funds may be used for buying books, journal subscriptions, travel to medical meetings, etc. When most clinical drug studies were conducted in academic settings, the major ethical dilemma was that young researchers would withhold pertinent information, such as other therapeutic choices, from the patients in order to facilitate their academic ambitions. Thus current safeguards in human research are all directed at curbing "academic" excesses through a system of peer review of study design and the adequacy of the consent form.

The ethical problems in CROs are quite different. As clinical research has moved into the private sector, competitive market pressures have escalated reimbursements to "volunteers", creating a shadow economy of professional human guinea pigs. The article summarised above is based on results of investigative journalism and not a comprehensive study of CROs. Indeed, to the best of my knowledge, no independent studies of the CRO industry have been conducted. Perhaps, it is too young an industry. The compulsions of protecting trade secrets may be an additional factor. The anecdotal news reports clearly indicate the need for a formal study of CRO ethics and practices.

Based on perhaps the same news reports, Elliott and Abadie (1) focus on the ethical dilemma: is it ethical to pay the poor to participate in clinical research? While such payments, designed to reimburse legitimate costs of participation, are allowed by regulators, Elliott and Abadie feel that the current system is exploitative and "... contravene article 19 of the Declaration of Helsinki, which states that medical research is ethically justified only if there is a reasonable chance that the population ... will benefit from the results." They reiterate the lack of regulatory oversight: US law does not extend to multinational studies; the FDA only reviews about one per cent of the studies; IRBs are designed only to review the trial design, the risk-benefit ratio and the informed consent form; etc. Clearly, IRBs cannot monitor the kinds of abuses: "... fraud, conflicts of interest, unfair payment practices, and unsafe or degrading trial conditions." (1) In the case of the CROs, failure to adhere to ethical standards may or may not necessarily vitiate the results and scientific utility of a study, depending on the drug and the conditions. When the guinea pigs, to earn a living, "volunteer" for one study after another without giving adequate time for a washout of previous study drugs, do not inform the investigator of any underlying medical problems, etc., study findings may be invalid.

Are CROs necessary? Undoubtedly yes! Given the volume of new drugs being developed, I doubt if the universities have the time, the personnel or the inclination to carry out the number of phase 1 studies needed.

India, along with many other less developed countries, has limited access to health care that is affordable; thus it provides a large pool of potential subjects for clinical pharmacologic research. The cost of conducting a trial in India is 30-50 per cent less than in the US. But more important than monetary advantage is the availability of a large pool of drug naïve

subjects (2). With news media allegations of exploitation of uneducated and illiterate subjects in India, it is important to consider what can be done to assure high ethical standards in conduct of trials. Barnes (3) lists several measures that the industry can adopt. These include careful site selection, selection of investigators who understand good clinical practice, ethics of drug research including the consent process and the need for scrupulous documentation of the consent. Consent forms must be in a language the patient understands and must be clearly explained to the patient who must be given time to assimilate the information.

Many of the problems cited above could be addressed by accepting the commercial nature of the CROs and developing safeguards for the "volunteers". In India, as much as in the US, the role of the IRBs needs to be expanded to verify and assure environmental sanitation and personal safety of the "volunteers." To assure the physical safety and environment concerns, all CROs should be designated as free standing health centres and be required to be accredited by a JCAHO-type accreditation process. Extending a "professional" designation to these volunteers and organising them into a guild of registered clinical research subjects, may give the group collective bargaining rights, access to affordable health and disability insurance, etc. Phase 1 trials do not need to be "mild torture economy" where the subjects are "paid to endure." (1)

References

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