

**Drug Development and the Ethics
of the Globalized Clinical Trial**

Adriana Petryna

The Occasional Papers of the School of Social Science are versions of talks given at the School's weekly Thursday Seminar. At these seminars, Members present work-in-progress and then take questions. There is often lively conversation and debate, some of which will be included with the papers. We have chosen papers we thought would be of interest to a broad audience. Our aim is to capture some part of the cross-disciplinary conversations that are the mark of the School's programs. While members are drawn from specific disciplines of the social sciences—anthropology, economics, sociology and political science—as well as history, philosophy, literature and law, the School encourages new approaches that arise from exposure to different forms of interpretation. The papers in this series differ widely in their topics, methods, and disciplines. Yet they concur in a broadly humanistic attempt to understand how, and under what conditions, the concepts that order experience in different cultures and societies are produced, and how they change.

Adriana Petryna is an Assistant Professor of Anthropology at The New School. She participated in the School of Social Science's year on bio-medical ethics, the third year of its focus on ethics. The emergence, in the previous two decades, of a specialty such as bioethics signals a turn toward analytical issues whose questions have less to do with the moral status of the social sciences than with the moral issues that arise within medicine considered as a social practice. Members during this year examined the ways in which medical technologies (drugs, procedures, diagnostics, genetic testing and engineering, surgeries) have changed or eroded the boundaries between public and private, and so raised new dilemmas for the law, public policy, and individual rights.

Dr. Petryna's ethnographic research explores science and medicine in Eastern Europe and in the United States. Her earlier work had focused on the Chernobyl nuclear disaster and this led her (as this paper will describe) to an investigation of U.S.-based pharmaceutical research. She is interested in the ways that cultural values and political and economic practices affect scientific production, and the concomitant effect of this production on governance and citizenship claims. Her first book, *Life Exposed: Biological Citizens after Chernobyl* (Princeton 2002), is an ethnographic examination of the vexed scientific and political circumstances that followed the nuclear disaster in then Soviet Ukraine. It was awarded the 2003 Sharon Stephens First Book Prize of the American Ethnological Society. Her current research focuses on commercialized clinical trials and their ethical and regulatory environments as they contribute to an expansion of human subjects involvement in research. She is co-editor of *Global Pharmaceuticals: Ethics, Markets, Practices* (Duke 2006), and is completing an ethnography of the evolving clinical trials industry.

Drug Development and the Ethics of the Globalized Clinical Trial

Since the early 1990s there has been a massive growth in the number of people participating in and required for pharmaceutical clinical trials. What drives this demand for larger pools of human subjects? First, it is the sheer number of trials being run. One market research company estimates that as of 2000, there were about 7,500 new clinical projects being designed for research and development worldwide. By 2001, that number had purportedly grown to 10,000 (Brescia 2002).¹ Second, to satisfy U.S. regulatory demands, increasingly large numbers of patients must be included in clinical trials to prove products' long-term safety, especially for drugs intended for a wide distribution. Third, some therapeutic categories—such as hypertension—are being overwhelmed with new drugs. Competition to get these drugs approved and to bring them to market intensifies the search for subjects. Fourth, there is a “drug pipeline explosion”—patent applications are flooding the U. S. Patent Office for new compounds that have yet to be clinically tested. Fifth, shifts in the very science of drug development also influence the decision to increase subject recruitment. As new potential molecular therapeutics are generated, making correct decisions about which molecules to test becomes more difficult. Consider the example of *antisense*, a technology made up of genetic snippets that infiltrate cells and prevent the expression of certain harmful proteins. When Wall Street investors learned that the technology showed signs of failing in a late-phase clinical trial for patients with skin cancer, researchers expanded the pool of subjects in an effort to find a statistically significant positive result.

Finally, the available pool of human subjects in the United States is shrinking. The generally affluent U.S. population is using too many drugs. “Treatment saturation” is making Americans increasingly unusable from a drug-testing standpoint. Our saturated bodies produce too many drug–drug interactions, providing less and less capacity to show drug effectiveness and making test results less statistically reliable. Indeed, however many Americans are ready to provide themselves as human subjects, whether from a belief in scientific progress, altruism, or therapeutic need, it will never be enough to satisfy the current level of demand for human subjects in commercial science. Because Americans cannot satisfy the need, the human subject research imperative is being pushed to other shores.

My work in progress considers the evolution of commercialized clinical trials and their concomitant ethical and regulatory environments as they contribute to a dramatic growth of human subjects involvement in research. Specifically, I focus on the operations of North American contract research organizations (or CROs), a specialized industry focusing on human subjects research that began listing and selling securities on public exchanges in the early 1990s. Clinical research in the United States has begun moving out of academic medical settings, where it had been principally conducted, to everyday hospital and primary care settings. It is also migrating globally to so-called non-traditional research areas—countries experiencing demographic change associated with declining health resources but having little or no share in the global pharmaceutical market.² CRO customers are pharmaceutical companies that, in selecting a CRO, weigh the cost of a study, its quality, and timeliness.³ I consider how these commercial actors interact with regulatory bodies, in the United States and abroad, with particular attention to the ways drug testing is expedited to low-income contexts. The geography of pharmaceutical

research and trial participation is changing. How it changes, and how “ethics” are configured alongside it to justify a massive expansion of commercialized human subjects research, is what this work is about.

CROs promise to locate research sites, recruit patients and, in some cases, draw up the study design and perform analyses. They claim that they can perform these functions more quickly and more cheaply than academic medical centers. In managing clinical trial sites, CROs sometimes work with site management organizations, which may include primary health care facilities, general practitioner networks, hospitals, or consortia of specialists focusing on a particular therapeutic area. CROs often affiliate themselves with site management organizations in countries in Eastern Europe, Latin America, the Middle East, and Africa, among others. Some even have their own centralized IRBs for single-investigator trials or for multi-center trials that can involve studies of up to 10,000 people in 10–20 countries. IRBs are, ideally, independent boards that are composed of scientific and nonscientific members whose duty is to ensure the safety of patients in a trial. Their purpose is to review and approve the trial protocol and methods to be used in obtaining and documenting the informed consent of trial subjects. The ethics committee model for monitoring the conduct of research, as sociologists and anthropologists of bioethics have noted, turns the ethical universe in which researchers operate into an essentially procedural one (Bosk 1999, 2002, 2005; Bosk and de Vries 2004; de Vries 2004; Guillemin 1998) and deflects attention from structural circumstances that can contribute to increased risk and injustice (Chambliss 1996; Marshall and Koenig 2004; Kahn et al.). Their commercialization also poses problems concerning credibility and necessary independence.⁴

The globalization of pharmaceutical trials is not only driven by the industry’s needs. During my field research in the mid- to late 1990s on the aftermath of Chernobyl (Petryna 2002), I observed a rapid growth of pharmaceutical markets in Ukraine and its neighboring countries. Working in government-operated research clinics and hospitals, I listened as physicians who tended to Chernobyl victims told me how anxious they were to learn how to do and to attract clinical trial contracts not only because of the abundance of various untreated diseases with which they were confronted, but also especially because the scientific infrastructures upon which they were dependent were quickly deteriorating without state funding. As local public health structures crumbled, international commercial and scientific interest was rising: this led to the sudden revaluation of patients who themselves had lost state protection in the form of guaranteed health care.⁵ It was not quite the dream “of Neel, Chagnon, and their gold-rush, tourist-hunting allies ‘to turn the Yanomami’s homeland into the world’s largest private reserve,’ a six-thousand- square-mile research station and ‘biosphere’ administered by themselves” (Geertz 2001:21).⁶ But scientists’ rush to reconceptualize their object of study “not as a people but as a population” to be brokered as valued research subjects on the pharmaceutical world scene was certainly there. This complex of circumstances led me to look carefully at the dimensions of regulatory and ethical change in the U.S. and abroad. In my ethnographic work with various professionals within the contract research organization (CRO) community (including company founders, CEOs, clinical trial managers, and health economists), the nurses and physicians with whom CROs contract, and pharmaceutical consultants and regulators in various countries, I came to see that the global dynamics of drug production play an important role in shaping the contexts in which ethical norms, and the delineations of human subjects, are changing.

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Currently a turf war is raging among pharmaceutical sponsors for human subjects. The competition relates not only to the numbers of subjects a given company can recruit, but to the speed with which they are recruited. As one veteran recruiter told me, “It’s really a problem. I don’t

know anybody who has really cracked the code. Sometimes you get lucky and you fill the study quickly, but for the most part, patients are really difficult to find, and they are difficult to find because everybody is looking for them.” Companies now scan the world, statistically and innovatively carving out new populations for larger and more complicated trials to assess the drug safety and efficacy demanded by U.S. regulators and consumers.⁷ Eastern Europe is seen as a particularly good recruitment site: given the collapse of basic health care there, patient enrollment in clinical trials is said to be quick. Post-socialist health care systems are conducive to running efficient trials because they remain centralized. High literacy rates in these areas mean that subjects offer more “meaningful” informed consent, thus smoothing potential regulatory setbacks in the future.⁸ Large Latin American cities such as Lima and São Paulo are also considered premier sites because, as one CRO-based recruiter told me, “Populations are massive. It’s a question of how many patients I can get within a limited area which reduces travel cost.” According to him, CROs battle over “who gets those patients, who I can sign up to be in my alliance so that when I do attract a sponsor, I can say ‘I can line up five hundred cancer patients for you tomorrow morning.’ You are seeing that happening a lot because recruitment is one of the most time consuming and expensive portions of the plan.”

Eastern Europe and Latin America are particularly attractive because of the abundance of so-called treatment naïveté: the widespread absence of treatment for common and uncommon diseases. Treatment naïve populations are considered valuable because they do not have any background medication, or any medication, for that matter, that may obscure the effect of a tested drug. CROs make themselves competitive by locating these special populations. As one researcher told me, these populations “offer a more likely prospect of minimizing the number of variables affecting results and a better chance of showing drug effectiveness.”⁹

On the one hand, pharmaceutical markets are expanding. On the other hand, drug developers are now focusing on the biology of populations experiencing acute health care crises—populations whose life expectancies increased and whose incidence of infectious disease and mortality rates decreased under the so-called health transition, but whose lives are now shorter, more chronically diseased, and less socially protected.¹⁰ The public health tactic of demarcating disease to prevent disease (involving epidemiology, prevention, and medical access) is now used to carve out new catchment areas of human subjects who are targeted precisely because of their treatment naïveté. This move may appear exploitative in itself, but the pharmaceutical industry argues that it is positive insofar as, in these regions, clinical trials have become social goods in themselves. And they may well be providing health care where there is little (Whyte 2006) and allowing medical relief for participants’ specific ailments for the duration of the trial.

Such facts raise difficult questions about how groups worldwide become participants in the dynamics of pharmaceutical innovation, and how and on what terms (if any) they become recipients of its benefits. The drug revolution, accelerated by the biotechnology sector and health care crises, brings into analytic focus the problem of managing human research across a variety of political and economic spheres in the absence of clear legislation in the U.S. or any transnational regulatory policy.

Much bioethical discussion tends to focus critiques of such experimental orders almost exclusively on questions of clinical conduct and informed consent. In so doing, these discussions have narrowed our view of the complexity of emergent ethical dilemmas in the arena of global research as they have narrowed the possibilities of critique. As violations of individual bodily integrity in human research continue to be exposed in the media, social scientists are also challenged to chart and consider how whole populations are brought into experimental orders and why the available discourses and protective mechanisms are unable to intervene to assist these groups. In this era of globalized human research, the baseline conditions that would make a universal ethics applicable and enforceable worldwide are highly uneven. Indeed, I will argue that

the ethical arrangements that have grown up around populations and their diseases are made visible by examining the spatial and temporal complexities associated with the demands of drug research, and by analyzing the practices of CROs, among other organizations, that fill this demand.

This said, in what follows, I consider some key moments in the recent ethical and regulatory discussion of globalizing research in contexts of crisis. I'll show how crisis conditions and regulatory decisions legitimate variability in ethical standards in drug testing. In a commercialized pharmaceutical setting, such ethical variability evolves as a tactic informing the organization and movement of clinical trials. As context, I'll argue that the global conditions of human research (recruitment strategies and their inherent risks) cannot be understood without knowing what has happened to human research in the United States: we must look into some of the ordinary practices of research that point to systemic risk in the business of trials. I'll also discuss concrete examples of these practices, such as the so called "floater" or first time sites that make no investment in regulatory compliance but usually guarantee rapid recruitment for pharmaceutical sponsors. Such institutional formations affect the quality of the experiment and have implications for how experimental groups are being defined and pursued elsewhere.

Ethical Variability

The controversy over placebo use in Africa during the 1994 trials of short-course AZT treatment to halt perinatal transmission of HIV was a watershed in the debate over ethical standards in global clinical research.¹¹ In this well-known case, some U.S. researchers argued that giving less than standard care to those on the placebo arm of the study was ethically responsible, even if in the United States the standard of care medication was already known.¹² A placebo is an inactive treatment made to appear like real treatment; it amounts to no treatment. Critics viewed the use of a placebo arm in this case as highly unethical. They charged that research carried out in developing countries could be held to a standard that differs from requirements in developed countries. Marcia Angell (2000), for example, noted patterns of conduct reminiscent of the Tuskegee syphilis experiment, in which low-income communities provide standing reserves of exploitable research subjects. In defense of the study, Harold Varmus of the National Institutes of Health (NIH) and David Satcher of the Centers for Disease Control, which, among other government institutions, authorized and funded the trial, claimed that the trial was ethically sound (Varmus and Satcher 1996). They cited local cultural variables and deteriorating health infrastructures as factors making the delivery of the best standard of care infeasible. It would be a paternalistic imposition, they argued, for critics in the United States to determine the appropriate design of medical research in a region undergoing a massive health crisis and that deciding the appropriate conduct of research and treatment distribution was within the jurisdiction of local and national authorities.

Ethical imperialism or ethical relativism? The debate, as it stands, remains unresolved. Yet these catch phrases represent current responses to the ethics of the trial. The first position builds on known histories of marginalized communities acting as human subjects, a history, as medical historian Harry Marks suggests, that may obscure more than it reveals about the circumstances of experimental communities today.¹³ The second position relativizes ethical decision-making as a matter of sound science, but it fails to consider the uptake of this relativizing move in corporate research contexts. To my eye, the facts of the African trial—and the ethical debates that followed it—highlight the role that crisis plays in any consideration of differences in ethical standards in the area of human research; indeed, *in extremis*, crisis conditions legitimate variability in ethical standards.¹⁴ Historically, some crises have led, perhaps inescapably, to experimentation. But one can ask: Are crisis states the exception or are they the norm? To what extent does the language of crisis become instrumental, granting legitimacy to

experimentation when it otherwise might not have any?

The debate over the ethics of the AZT trial prompted the sixth revision of the Helsinki Declaration first issued in 1964. The declaration deals with “all aspects of human biomedical research, providing guidelines for investigators to follow in research involving human subjects.”¹⁵ The 2000 revision reiterated a position against placebo use when standards of treatment are known: “The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists.”¹⁶ If the ethics were unambiguous, the regulatory weight of the Declaration was not. In this latter domain, the winners and losers of the placebo debate would be named. Pharmaceutical companies, already eagerly expanding operations abroad and calculating the economic advantages of placebo use—placebos lower costs and, many argue, placebo trials produce more unambiguous evidence of efficacy—were scrambling to learn from regulators about the legal enforceability of the Declaration while finding ways to continue using the placebo.

Haziness brought clarification of the rules of the game. Robert Temple, an influential regulator in the Center for Drug Evaluation of the U.S. Food and Drug Administration, undercut the regulatory significance of the Declaration and threw his support behind placebo advocates. He cited the International Conference on Harmonization (ICH-E10 2001) as the alternative and more authoritative guideline on the ethics of placebo use. This guideline states, “Whether a particular placebo controlled trial of a new agent will be acceptable to subjects and investigators when there is a known effective therapy is a matter of patient, investigator, and IRB judgment, and acceptability may differ among ICH regions. Acceptability could depend on the specific trial design and *population chosen*” (Temple 2002:213, emphasis added). In other words, the ethical standard for the world was claimed to be variability.

Temple’s support for the placebo trial was ostensibly guided by a concern for generating high quality scientific data. His reaction is also indicative of how regulatory regimes can influence the definition of experimental groups. The alternative to the placebo-control is the active-control trial. Its purpose is to compare a new drug with a standard one, to show the superiority of the new drug to the active control, or to at least show a difference.¹⁷ With active controls, an increased chance for study defects that may invalidate the data is possible: these include poor patient compliance, poor diagnostic practice, and the use of concomitant medications on the part of the patient that can hinder the assessment of the drug’s effect. Following this logic, the treatment naïve are more foolproof and valuable research subjects precisely because they are often poor and do not have access to treatment. Other defects can include inconsistencies in the application of definition of disease, the use of insensitive or inappropriate measures of drug effectiveness, and the chance of spontaneous recovery in a study population. These factors can decrease difference or increase the chances of finding no difference such that, in the end, in Temple’s words, “you don’t know if either of them worked” (Vastag 2000:2984). By contrast, a placebo-control trial is capable of showing difference and, much more importantly, it is able to discern effective and ineffective treatments. Such ability is considered a key marker of reliable evidence of the effectiveness of a new drug. Active control trials fail to make such a distinction and are therefore not preferable from a regulatory standpoint. Temple’s invalidation of the active-control trial is anthropologically and economically significant—the treatment naïve become preferable from a regulatory standpoint that emphasizes the importance of an efficient (and foolproof) global research subject.

In responding to the Helsinki Declaration revision, U.S. regulators sent a strong signal to industrial drug developers that their leading concern was research efficiency. They let it be understood that the murky ethics of placebo use could be bypassed by providing for what is known as equivalent medication: not necessarily the best or standard treatment, but the best

available local equivalent. As one researcher put it cynically, “Do I give them a sugar pill or vitamin C?” In such a case, the study will be ethical, the data will have integrity and, sadly, the patients will remain treatment naïve. Another researcher echoed this sense that there has been a shift from concerns about fairness to efficiency-based standards in global research when he told me that ethics came to be seen as a “workable document”: “Equivalent medication in Eastern Europe is not the same as equivalent medication in Western Europe, so you could work the Helsinki Declaration.”

In tracing the relation between regulation and the making of ethics in human research, Harry Marks notes: “It is as if ethical discourse and the regulations governing research exist in two parallel universes which share some common elements but do not connect” (2000:14). But I would argue that the aftermath of the 1994 AZT trials demonstrates how connected those universes are, and how regulatory decision-making at the transnational level encourages the evolution of “local” experimental terrains. Regulatory response in the context of debates over the Helsinki Declaration’s revision (which itself was a response to controversial uses of human subjects) is itself instantiating new populations of human subjects—the treatment naïve.

The treatment naïve remain variably protected under current regulatory configurations of ethics. I say “variably” because some national governments faced with a sudden growth of human subjects research have minimal bureaucracies to cope with their oversight. Some might know little about structures of liability in cases of adverse or catastrophic events.¹⁸ Nor might they have the bargaining power or be particularly interested in pressing for fairer procedures and access to drugs during and after the trial. Thus there is a distinction to be made between ethical codes (in which the definition of what constitutes biomedical harm is fairly unambiguous) and ethical regulation (in which deliberation of those definitions are balanced against economic, scientific, and regulatory constraints and demands). Ethical regulation entails set procedures governing proper human research as inscribed in public policy and law. It is also a realm of contingent practice, and the allocation of protection for human subjects research is far from settled here.

Growth of Global Subjects Research

Starting in the early 90s, just four years before the controversial AZT trials, the FDA began to actively promote the globalization of commercial clinical trials (Office of the Inspector General, Department of Health and Human Services 2001:42). The International Conference on Harmonization guidelines or ICH was established. The ICH allowed findings from pharmaceutical research carried out in multi-national settings to be transferred and submitted to the FDA for approval for use (and sale) of their new drugs in mainly North American and European markets. Participation in U.S.-sponsored research swelled among clinical investigators who were pursued by pharmaceutical representatives in countries that had voluntarily agreed to harmonizing standards in the field of commercial drug testing: Argentina, Brazil, Hungary, Mexico, Poland, Russia, and Thailand, among others. As a result, the number of international human subjects involved in clinical trials grew dramatically between 1995 and 1999: from 4,000 in 1995 to 400,000 in 1999.¹⁹

This global growth of research brought with it a new set of unknowns about the circumstances in which research was conducted, and concerns about the possible exploitation of foreign subjects. Regulatory response was, as I’ve indicated throughout, uneven: there have been many proposals for improving the system of monitoring trials, but little on matters of social justice and fair distribution (Kahn et al. 1998). In 1999, the Office of the Inspector General, a body that carries out periodic reviews of the FDA, told that agency after careful review that, “in spite of its active promotion of the search for sites and subjects elsewhere,” the FDA is not able to protect human subjects in research elsewhere.²⁰ It recommended that the FDA support and, in

some cases help to construct, local ethical review boards.

In 2000, the National Bioethics Advisory Commission (NBAC) recommended that studies submitted to the FDA receive ethical committee review both in the United States and in the country in which research was being carried out (as opposed to the present situation in which only foreign ethical review and approval is required). It endorsed the idea of dual review with the provision that if host countries have working ethical review committees, only this type of approval is required.

Approaches involving monitoring, data collection, and more local ethics committees lean heavily towards what political theorist Iris Young (2004) calls a liability model of accountability: if one names the responsible local parties (or, in some cases, first sets them up) then surely they can gather information and make the right decisions; surely they can stop inappropriate research from taking place. A functioning state and legal system is assumed. Much is also assumed about who is and isn't the agent of abuse, most typically defined as the individual investigator himself. This leaves little room to account for instances in which risks present themselves in a more structural form. The fact is that certain conditions have to be met in order for liability to work: states themselves need to act as protectors and not abusers; transnational corporations need not only to respect the rights and dignity of all research subjects, but to recognize the fact that different situations elicit different levels of threat and coercion. International laws must be enforceable in the case of violations.

Unfortunately, none of these conditions were met in a 1996 case in which U.S. industry-sponsored research was conducted in Nigeria for a drug called Trovan, an antibiotic, widely prescribed, but later taken off the market because it was found to have serious liver side effects. The trial protocol for a new use of Trovan was not approved by a U.S. ethics committee and received a grossly inadequate if nonexistent review in the host country. Lawyers of the Nigerian plaintiffs charged a top pharmaceutical company in the deaths of 11 children, who were among 100 children to have participated in a clinical trial for meningitis treatments in the context of a massive outbreak of bacterial meningitis during civil war. Some children were given Trovan in a form never tested on humans before; others were given a lowered dose of the standard of care for meningitis that, according to the complaint filed by the New York law firm of Milberg Weiss on behalf of the parents of these children, allowed researchers to show that Trovan was more efficacious. This low dosing, the plaintiffs claimed, resulted in the deaths of the 11 children. The research team is alleged to not have explained the experimental nature of Trovan to subjects; parents believed their children were receiving a proven treatment.²¹

This is one of the first cases brought by foreign subjects against a multi-national pharmaceutical company. Legal documents show that informed consent forms used in the defense are backdated. The plaintiff's lawyers suggest a chain of complicity in making the children available for research that includes Nigeria's military rulers and state officials, Ministry of Health officials, and local hospital administrators; U.S. FDA regulators who authorized an unapproved drug's export to Nigeria for humanitarian purposes, and Pfizer researchers who selected their subjects from a line of children waiting for standard treatments.

The fact that this case is well publicized does not mean that the actions of other wrongdoers will be regulated or prosecuted. In similar cases, federal judges have ruled that internationally accepted codes of human subjects protection (in this case the Nuremberg Code and the Helsinki Declaration), cannot be relied upon as the basis of civil suits in U.S. courts. In this case, even if there had been a functional ethical review of U.S. industry-sponsored research, the tragedy might not have been prevented so long as Nigerian interests were not on the side of protection but, overwhelmingly, on the side of making populations accessible to research.

Floater Sites

The demand for human subjects in developing countries cannot be understood without some knowledge about what is happening domestically in the United States. One point of origin in the commercial expansion of trials dates back to the early 1970s, when the use of prisoner subjects in the U.S. was exposed and severely criticized. The scale of U.S. prison research was impressive: an estimated ninety percent of Phase One drug testing was conducted using prison populations (Harkness 1996).²² When the 1980 ban on use of prisoners finally set in (for particular phases of testing), pharmaceutical companies lost almost an entire base of human volunteers and shifted a good deal of their research elsewhere, namely, to Europe (and countries with regulatory-friendly environments), but also to other areas with large subject pools whose access could be guaranteed because of centralized health systems and the closed nature of referral systems. But advocates of prison research claimed that something was forever lost too: the ability to test for adverse reactions to drugs (especially among recidivist prisoners). What was called “liability testing” had been foreclosed and remains the most underdeveloped aspect of drug testing. Many industry people attribute rising drug costs in part to the rise in harmful adverse drug effects and product liability. One informant, who directs the international clinical trial division of a major CRO, is often frustrated with the kinds of tasks his team is asked to perform. He said, “In any industrial system, if you spend 10 times as much on repair as on prevention, you are just going to live in a continued cycle [of loss]. I’ll just say that for every dollar spent on an investigation, 10 dollars is spent on going back and fixing the data after the fact.” I’ll address how fixing data relates to the concept of “rescue” in clinical studies shortly.

By the 1970s and 80s, drugs were tested largely on populations in the U.S. and Western Europe in academic medical settings. By the early 90s, after the “drug pipeline explosion” referred to earlier, there was an over-demand for such sites. New recruitment strategies outside tried and true academic research sites and new venues (including private health organizations) were pursued. So productive was this new terrain that pharmaceutical companies and CROs now even prefer physician and group practices and primary care centers to academic medical centers.

The outline of the structure of sponsorship and recruitment for clinical trials in the U.S., in cases where a third party (CRO) is involved, may shed some further light on the movement of research overseas. At the first level, there are the pharmaceutical companies or the sponsors who have a new molecule to test. Let’s say they want to outsource the development of that entity to a CRO (second level), which in turn handles aspects related to recruitment, testing, and approval. At a third level, there is the investigator and the investigator site, which may be a hospital, a physician group practice, or an academic institution. The number of group physicians and primary care doctors interested in transforming their practices into investigator sites increased dramatically in the last ten years. This interest was a response to lowered Medicare reimbursements and changes in the structure of payments by HMOs. Doctors turned to clinical trials as a possible way of recouping some of their shrinking profits. Specialized businesses were also founded, mainly by people who left large academic medical institutions after they gained sponsor-investigator coordinating skills. Many nurses, for example, ran into conflict with academic administrators in attempting to bring in more industry sponsored clinical research.

But profits often did not quite materialize. Members of the CRO community complain that, despite high development costs of a drug, their customers—pharmaceutical companies—have kept payments to CROs flat. Investigator sites in turn complain that payments are not in step with nurses’ salary inflation and the high cost of making sure that sites are regulatorily compliant (which involves costs such as the completion of paperwork, the reporting of adverse events to the FDA, the documentation of informed consent, etc.). These economics have led to the

pervasive problem of the so-called floater site, sites that promise many patients, routinely underbid for contracts, and are not particularly concerned with achieving standards of full compliance. They make their money and disappear from the clinical trial food chain.²³ Their existence lowers the profitability of clinical research in the United States.

Even in highly regulated systems, windows of opportunity can be exploited until new regulations come into place. One very real factor pushing the transition of research into developing countries is this attempt to skirt the effects of regulation whether it takes the form of a pursuit for more floaters (which some CROs do pursue) or as an escape from the problems imposed in this country such as uncertain liability and behaviors that ensue from flat payment structures (the overbooking of study sites and nurse and personnel burn-out are examples).

This view into the ordinary practices of human research requires more study; my sketch is intended to make more concrete the broader empirical question of how commercial pressures change the very forms of scientific experimentation, and how potential systemic harms are generated through everyday practices that can elude the dictates of written protocols. The FDA Office of Compliance notes a seventeen fold increase since 1998 in the number of complaints filed against investigators, and this increase is attributed to protocol violations, falsification of data, informed consent noncompliance, and poor adverse event reporting.

Add the reality of the rescue trial to the mix, and you'll begin to have a clearer picture of how these domestic issues affect global clinical trials. The term "rescue" applies to a study that begins in one location and, because of poor recruitment, is shifted to another location midway through the trial. Some trials that were initially launched in Western Europe, for example, were shifted to Eastern European countries (commonly referred to as "rescue countries" in the early to mid 90s). The term can also refer to a study that takes place when the life cycle of a new drug is suddenly cut short; the "rescue study" requires rapid patient enrollment and must be quickly set up. Studies of this sort can result from product failures (owing to adverse drug effects, for example), and they make up a significant amount of the international studies in which CROs are engaged.

Trovan was one such case. Unforeseen adverse effects—in the form of liver failures—led to the drug losing its licensing. The stock market value of the would-be blockbuster plummeted. At this precise moment, the sponsor put out bids to CROs to find other uses for Trovan which would allow the company to at least recoup some of the investment cost in the drug. Besides Nigeria, there was a research protocol in the United States to test Trovan for treating intra-abdominal infection stemming from ruptured appendices which also required the recruitment of many patients quickly. One bidder explained to me why his CRO lost to another: "Whereas we went to the tried and true sites for patient enrollment [that is, the non-floaters], they went to the Southwestern United States, to a ring of facilities in order to enroll trial subjects. By going to a Southwestern hospital chain treating Hispanics with little or no medical insurance, this second CRO far outstripped us in enrollment."

The fact that most of these Hispanics were on limited (capitated) health insurance plans helped increase the numbers of people who were recruited. The losing bidder also explained to me that this site helped generate subjects peculiarly appropriate for testing in this case: as a general rule, a disproportionate amount of people with capitated HMO are prone to a burst appendix. "You can call your doctor on a Saturday night and say 'Doctor, I have a sore belly.' And he says, 'don't go to the emergency room, I'll see you on Monday in my office.' The infection is induced. That is precisely what happened here." This informant tells me that this kind of tampering with an acute condition is not an uncommon story in the world of human subjects research today.

Some clinical researchers with whom I spoke in Brazil are watching as pharmaceutical companies and CROs begin to substantially influence the course of research in the country. They express a lack of confidence about the biological significance of some of the new drugs they

are asked to test on their patients. Issues of social justice are at stake when new drugs do not promise to cure or extend life but simply to lower a non-clinical indicator, such as reduced virological response (as in some hepatitis C treatments). While this is a typical problem everywhere, what happens in this socio-economic context is that when the new drugs come on the market, they can be twenty times more expensive than the standard, and massively redirect state financing of health care to only a few.²⁴

If it is indeed true that ten times more money is spent on repair than on prevention in some pharmaceutical drug trials, the question becomes whether we want to spend so much money on the repair of drugs or the creation of drugs with relatively small benefits. Are there better commercial research paradigms that can promote fairness and equal forms of protection and health? Floater sites and rescue studies explicate concrete topological and ethical dimensions of the commercial global research imperative and how that research imperative unevenly distributes medical possibilities and health worldwide.

Where industry and regulatory concerns about ethics currently seem most pressing is at the level of the data—more specifically, at the level of insuring the “integrity” of research data. Why invest in a foreign site, already potentially fraught with liabilities, if one is uncertain about whether this data will be usable in the U.S. drug approval process? This, I believe, is partly driving the push to establish more local ethical review boards in newer sites. Was there informed consent? Did the local investigator agree to accept all responsibility in case of an adverse reaction or death? Did the local ethical review board review and ok the protocol? At stake is the construction of a weatherproof documentary environment insuring the portability of foreign-derived data, even if that data was derived in the middle of an epidemic or in a war zone.

In the early 1970s, when the scandal over the use of prison subjects broke, the FDA claimed it had little documentation, citing its duty to protect intellectual property. Today the FDA resists gathering data on the out-migration of human research, on the basis that location of testing is proprietary information. One might want to rethink the question of whether anonymity of the sources of clinical research data remains a defensible idea.

Once more knowledge about the contexts of the production of pharmaceuticals evolves—the kinds of experiments and the human participants they involve—we may find ourselves in a better position too to rethink the criteria of what we take to be of technological and therapeutic significance, and, in the process, redirect our economic, moral, and scientific investments.

ENDNOTES

- 1 Estimates for the current number of clinical trials differ dramatically. For example, according to CenterWatch (2002), an information services company monitoring clinical research, 80,000 clinical trials were underway in the United States alone in 2002 (this number is routinely quoted in industry literature). However, an industry informant believes the 80,000 number is too high. He noted that it is next to impossible to give an estimate of clinical trials worldwide, because there is no central repository. Instead, this informant suggests the following: “that there are between 25,000 - 40,000 clinical trials conducted in the U.S. alone,” and that “other sources indicate 80,000 for the US - but others believe that the 80,000 represents the number of clinical trials globally.” Such ambiguity in numerical estimates suggests a global field of experimental activity whose true scope is largely unknown and prone to guesswork. Estimating the number of clinical trials is an inexact science to say the least. Dickersin and Rennie (2003:516) suggest major barriers to a comprehensive repository of clinical trials, including “industry resistance, the lack of a funding appropriation for a serious and sustained effort, lack of a mechanism for enforcement of policies, and lack of awareness of the importance of the problem.”
- 2 Among the 10 leading global pharmaceutical markets, the United States ranks first and holds a 60.5 percent share. Germany, France, Italy, the UK, Spain, and Belgium also rank among the top ten. Combined, they hold a 21% percent share, followed by Japan (15.1%), Canada (2.4%), and Australia (1.1%) (<http://www.imshealth.com>). The Office of Inspector General, Department of Health and Human Services, states that “among the countries that have experiences the largest growth in clinical investigators [for commercially sponsored trials] are Russia and countries in Eastern Europe and Latin America” (2001:i). The clinical trial industry is actively moving operations to China as well.
- 3 Elements considered in cost-effective trial siting include local levels of unemployment, population disease profiles, morbidity and mortality rates, and per-patient trial costs and potential for future marketing of the approved drug. CROs investigate the host country’s regulatory environment. They ask whether universal access to health is in place. They assess regulatory priorities and capacities of host countries (e.g., efficacy of local ethical review boards and outlooks and regulations on placebo use).
- 4 For an assessment of the commercialization of ethical review boards, see T. Lemmens and B. Freedman, “Ethics Review for Sale? Conflict of Interest and Commercial Research Ethics Review.” *Milbank Quarterly* (2000) 78(4): 547-584.
- 5 Take for instance these statements from a marketing report of a small Russian-based contract research organization. “The Russian Federation is a country of 145 million people. Although about 65% of the population lives in industrialised cities with access to government-sponsored medical care and treatment centres, the country has been mired in a negative population growth for over 10 years.” Compared with mortality rates in Japan, Western

Europe, and North America, where over the last 40 years cardiovascular disease and strokes have fallen sharply, “Russia, by contrast, suffered an explosion of cardiovascular deaths over the same period.” The report projects a sense of societal mortal danger, “there is little hope that the government [. . .] will be able to incorporate enough changes [to its limited infrastructure] to slow or stop the trend.” With the lack of a functioning pharmaceutical market or state to lower mortality rates, the trend of disease and harm is unstoppable. But because of these and other characteristics, Russia proves “a perfect platform for clinical research.”

- 6 Geertz’s quote continues: “The problem was that the anthros (and the *médicos*), reductionist to the core, conceived the object of their study not as a people but as a population. The Yanomami, who indeed had the requisite sorts of brains, eyes, and fingers, were a control group in an inquiry centered elsewhere.”
- 7 They typically rely on epidemiological data published by the World Health Organization and national health statistics.
- 8 Literacy is believed to provide assurances to any future potential auditor that the risks and benefits of research indicated in consent forms were understood when signed.
- 9 There are variations on the term treatment-naïve. Eastern European populations are referred to as “statin-naïve” and “steroid-naïve,” for example. The terms code for a lack of exposure to a particular compound, but also can refer to a group of people who have just been diagnosed (for hypertension, for example) but have never been treated. Finding this kind of group proves to be difficult in the United States and Western Europe, and increasingly so in Poland and East-Central Europe where pharmaceutical markets are growing. “We are heading to Uzbekistan and Central Asia,” according to a CRO executive who launched the Czech clinical trials market in the mid 90s. He sees the Czech market thriving for another ten years. One of the main indicators that such a market is losing its sustainability, according to this executive, is that people “will leave the trials.”
- 10 *Health transition* refers to the role that the cultural, social, and behavioral factors of health play in rising life expectancy at birth (the mortality transition) and the decreasing proportion of all deaths caused by infectious diseases (the epidemiological transition). “Studies of the health transition focus on the institutional aspects that promote such change including public health interventions that control disease and promote modern health care” (Johansson 1991:39).
- 11 See commentaries by Angell 1997, 2000; Bayer 1998; Benatar 2001; Benatar and Singer 2000; Botbol-Baum 2000; Crouch and Arras 1998; de Zulueta 2001; Lurie and Wolfe 1998, 2000; Rothman 2000; Schuklenk and Ashcroft 2000.
- 12 The placebo-control trial typically consists of a placebo arm and a treatment arm. Its alternative, the active-control trial consists of an arm of treatment with known efficacy (active control) and an experimental arm.
- 13 Marks and other scholars suggest the important role of “cooperative” patients and “professional guinea pigs” in the history of human subjects experimentation (Marks 2002; Harkness 1996).

- 14 Variability is not meant to evoke the notion of cultural relativism here, although variability has been considered in such terms (Christakis 1992). Reliance upon culture to explain differences in global health practices has been a central project in the field of medical anthropology for decades. Knowledge of such differences as translated into the health care arena tends to focus on “unbridgeable” moral divides between western and non-western cultures. In the ethical imperialism vs relativism debate (see Macklin 1999), anthropologists working in health arenas have been perceived as having a blind defense of local cultural tradition. See “Anti Anti-Relativism” by Clifford Geertz on the “moral and intellectual consequences that are commonly supposed to flow from relativism—subjectivism, nihilism, incoherence, Machiavellianism, ethical idiocy, esthetic blindness, and so on” (2000: 42). Medical anthropologists more recently contend that a focus on cultural and moral difference in health care has become dangerous to the very people and practices anthropologists have sought to explain, particularly in the contexts of massive epidemics and debates over treatment access. As anthropologist-physician Paul Farmer and others point out, culture has been used to explain “why” the poor are somehow less responsible regarding treatment regimes. The alarmingly slow development of the anti-HIV drug market in Africa, for example, has been attributed to the allegedly unreliable medical and economic behaviors of that continent’s desperately poor HIV sufferers. These characteristics are said to heighten investment risk that in turn justifies limited access to low-cost drugs. Anthropologist-physician Jim Yong Kim has discussed the way moral assumptions in health planning can further entrench inequality, justifying some interventions while disallowing others (Kim 1999). Other medical anthropologists have shown how the local trajectories of pandemics are influenced by the logic of international policy and choices (Das 1999, Cohen 1999, Biehl 2005). This latter body of work explores how differences in the organization of institutions authorized to deal with health problems (state bureaucracies, welfare agencies, insurance companies, medical facilities, and religious and humanitarian organizations) result in distinct programs and policies. These not only differ greatly in form and content, they also can shape different courses of health and disease and influence the outcomes of both (Petryna and Kleinman 2006). These works move beyond emphasis on difference in the health arena, and represent new empirical work addressing the ethical and political realities of emergent global drug markets.
- 15 The Declaration of Helsinki has been modified five times since its first edition in 1964.
- 16 This statement does not refer to cases in which risk from withholding a proven therapy is lacking, as, for instance in the case of analgesics and antihistamines.
- 17 To many patients and clinicians, this is the information of greatest relevance, namely, the comparative effectiveness of a new drug to a standard therapy.
- 18 CROs and pharmaceutical sponsors tell me that their greatest concern is liability. In Europe, for example, governments require CROs, pharmaceutical sponsors, or both, to purchase insurance. As one lawyer who arranges research contracts told me, “What if something goes wrong? What if the patient dies? What if there is some horrible side effect? Who is going to pay? That is big dollars. In the United States we have a legal system that we all understand, and the liability will be divided based upon negligence. That’s how our legal system works. But in all of these other countries you really have to think about who is going to be responsible. Some countries such as Italy, Spain, and Germany require clinical trial insurance. They

require the sponsors to purchase a local insurance policy so that they know that if patients get injured there will be money there to take care of them.” Things look different, however, in different parts of the world. At one recent conference (that brought together representatives of the human subjects research industry from all over the world), I watched as pharmaceutical industry representatives lobbied some developing country officials to avoid “the insurance path” and to rely on systems of universal health coverage to cover costs. Legislation is pending in Brazil that would require CROs to register with the state’s national health surveillance agency (ANVISA). According to one Brazilian official, this legislation is being put into place “because often what happens is that big pharmaceutical companies work through third-parties. The CRO comes in and, let’s say there is an adverse event, someone needs surgery, and the CRO is not held liable, even though the pharmaceutical company guarantees liability coverage.” This official put it very succinctly, “The patient/subject signs the informed consent form but the protection is a fiction. They are not insured.”

- 19 This number refers to new drug applications only. In Brazil, for example, the number of clinical investigators grew from 16 in 1991 to 187 in 1999. In Russia, the number grew from 0 in 1991 to 170 in 1999. In collaboration with the ICH, a harmonizing initiative is underway in the Americas called the Pan American Network for Drug Regulatory Harmonization. The European Union recently implemented the E.U. Clinical Trials Directive for E.U. countries and accession states.
- 20 The OIG’s mission statement is as follows: “The mission of the Office of Inspector General, as mandated by Public Law 95-452 (as amended), is to protect the integrity of Department of Health and Human Services (HHS) programs, as well as the health and welfare of the beneficiaries of those programs. The OIG has a responsibility to report both to the Secretary and to the Congress program and management problems and recommendations to correct them. The OIG’s duties are carried out through a nationwide network of audits, investigations, inspections and other mission-related functions performed by OIG components.” Office of Inspector General at the Department of Health and Human Services (<http://oig.hhs.gov/organization/OIGmission.html>).
- 21 The Trovan story illustrates how the political economy of drug development links seemingly disconnected worlds and jurisdictions. At the same time, the legal viability of existing international codes of human subjects protections is being thrown into doubt.
- 22 In 1980, the Food and Drug Administration established the 21 CFR 50.44 provision, which barred the use of prisoners as research subjects for Phase I safety testing.
- 23 Currently there is a move to license sites just like one would a dental office, but the industry is resisting this.
- 24 One public health administrator told me of an example in which the poor choice of an endpoint had important social ramifications which he continues to address and remediate. He referred me to the package insert of Peg-Intron, a state-of-the-art hepatitis C treatment employing a process called “pegylation,” whereby polyethylene glycol (PEG) is attached to a protein in order to extend the effects of the standard of care, Interferon. It states that the drug does not prevent cirrhosis or death or hepato-carcinoma (these are hard endpoints), “it just reduces virological response in six months.” In spite of little or no clinical evidence of

improvement, the drug was approved by the FDA, “and when the drug came to the Brazilian market, it was twenty times more expensive than the standard-of-care drug.” Comparing the high cost of Peg-Intron with the standard treatment, this administrator made a more compelling comparison between drugs and gold. “One gram of gold costs 34 *reals*. Ten dollars. One gram of diamonds, 134 *reals*. 40 dollars. One gram of Peg-Intron costs 400,000 *reals* today. One gram. With this one gram you can treat 110 patients, and you might prevent one liver cirrhosis. One cirrhosis in 110 patients, you *might* prevent it.”

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