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Ethical variability:

Drug development and globalizing clinical trials

ABSTRACT

The rapid growth of pharmaceutical markets has led to increased demands for human subjects for drug research, particularly in low-income countries. For regulatory, economic, and even biological reasons, new populations are being pursued as human subjects for pharmaceutical trials. In this article I consider the evolution of commercialized clinical trials and ethical and regulatory environments as they contribute to a dramatic growth of human-subjects involvement in research. I focus on the operations of U.S.-based contract research organizations (CROs), which make up a specialized global industry focusing on human-subjects recruitment and research and the on ways in which they expedite drug testing to low-income contexts. Specifically, I analyze how these transstate actors interact with regulatory authorities in the United States and how they recast international ethical guidelines as they organize trials for research subjects abroad. [global pharmaceuticals, bioethics, clinical trials, human subjects, research ethics, governance, biological citizenship]

Since the early 1990s, growth in the number of people participating in and required for pharmaceutical clinical trials has been massive. The number of clinical trial investigators conducting multinational drug research in low-income settings increased 16-fold in the past decade (Office of Inspector General, Department of Health and Human Services 2001), and the average annual growth rate of privately funded U.S. clinical trials recruiting subjects is projected to double by 2007.¹ Many of these new trials are being performed in geographical areas of political and economic instability and unprecedented health care crises and where subjects are readily accessible.² Drug companies' apparent ease of accessibility to such areas raises questions about the unequal social contexts in which research is being performed and about how conditions of inequality are at present facilitating a global proliferation of pharmaceutical drug trials.

Practical issues have overwhelmed ethics in terms of who governs international guidelines for ethical research and their capacity to protect the rights, interests, and well-being of human subjects globally (Benatar 2001; Benatar and Singer 2000; Farmer 2002; Lurie and Wolfe 2001; Office of Inspector General, Department of Health and Human Services 2001; Rothman 2000; Schuklenk and Ashcroft 2000). Social scientists have critiqued bioethicists for focusing discussions of new global experimental orders almost exclusively on procedural questions of informed consent and clinical conduct, narrowing the view of the complexity of emergent ethical dilemmas in the arena of global human-subjects research. Such a focus has led to a profound disconnect between bioethics—an abstract philosophical discourse grounding a set of codified norms for medical practice and research—and empirical reality.³ Arthur Kleinman (1999), for example, points to a “dangerous break” between bioethics and the realities of local moral worlds. Along this fault line of the moral and the ethical persons and their bodily integrity can be further damaged. Veena Das (1999) links international immunization programs and the manner of their implementation with the reemergence of local epidemics in India.

Her work raises questions about the relationship between bioethics and accountability in democratic societies and about the forms such ethics takes and to whom it is accountable.

Other anthropological work on the ethics of biotechnology and new medical technologies has shifted attention away from issues of individual autonomy and has deepened the analysis of new biomedical technologies as they affect new patterns of civic, medical, and commercial organization (Biehl 2001; Cohen 1999; DelVecchio Good 2001; Dumit 2000; Franklin 1995; Lock 2001; Petryna 2002; Rapp 1999; Scheper-Hughes 2004; Strathern 1992). This work examines an important dimension of ethics beyond its universal and regulatory (or normative) frameworks. New technologies raise new contexts of decision making over doing what is right; thus, beyond defining instances of moral certainty, ethics also involves a set of tactics that can be generative of new human conditions and events (Fischer 2001, 2003; Rabinow 1996, 2003).

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 contexts in which ethical norms and delineations of human subjects are changing. 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 the ways in which available discourses and protective mechanisms are unable to assist these groups and effectively intervene.

I also discovered an ethical variability at work in the globalization of trials, as one of several modes assisting pharmaceutical sponsors in mobilizing much larger populations of human subjects and in doing so much more quickly. *Ethical variability* refers to how international ethical guidelines (informed by principles and guidelines for research involving human subjects) are being recast as trials for global research subjects are organized.⁴ International standardized ethics has starkly failed to account for local contexts and lived experience (Cohen 1999; Das 1999; Kleinman 1999). In an industrial pharmaceutical context, ethical variability evolves as a tactic informing the regulation and organization of commercial clinical trials. It takes the specificities of local context and lived experience as a given and as a basis on which to consolidate a cost-effective variability in ethical standards in human research.

Variability, however, is not meant to evoke the notion of "cultural relativism," although variability has been interpreted in such terms (Christakis 1992). Reliance on

culture to explain differences in global health practices has been a central project in the field of medical anthropology for decades. Knowledge of such cultural differences, as translated into the health care arena, tends to focus on "unbridgeable" moral divides between Western and non-Western groups. In the ethical imperialism versus relativism debate (Macklin 1999), anthropologists working in health care arenas and elsewhere have been faulted for an alleged blind defense of local cultural tradition, making them susceptible to the "moral and intellectual consequences that are commonly supposed to flow from relativism—subjectivism, nihilism, incoherence, Machiavellianism, ethical idiocy, esthetic blindness, and so on" (Geertz 2000:42).

Medical anthropologists, by contrast, have recently contended that a strict focus on cultural and moral difference in health care has become dangerous to the very people and practices anthropologists have sought to understand, particularly in the contexts of massive epidemics and debates over treatment access. As Paul Farmer (1999), Jim Yong Kim et al. (2003), and others point out, culture understood as difference 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. Farmer and Kim et al. have shown the way moral assumptions in health planning can further entrench inequality, justifying some interventions while disallowing others.

Other anthropologists have moved beyond emphasis on difference and have shown, via careful ethnography, how trajectories of local pandemics are influenced by the logic of international policy and choices (Biehl 2001; Cohen 1999; Das 1999). 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 policies that not only differ in form and content but also can shape different courses of health and disease and influence the outcomes of both (Petryna and Kleinman in press).

These works point to the kind of empirical precision that is required to address the moral, ethical, and cultural realities of emergent global drug markets. In this article, I explore how ethical variability works, particularly in the conjuncture of accelerated drug development and the realities of global public health crises. I specify the effects of this variability on how human-subjects research is governed across various political and economic spheres, particularly in the absence of clear legislation in the United States and of transnational regulatory policy.⁵ Ethical variability has become central to the development and

global testing of pharmaceuticals and provides the means through which pharmaceutical sponsors and their third-party CROs achieve recruitment successes.

More human subjects

What drives the 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).⁶ 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 to be widely prescribed. 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.

Shifts in the very science of drug development also influence the decision to increase subject recruitment. As a vast amount of potential molecular therapeutics is generated, making right decisions regarding which molecules to test becomes more difficult. Consider Genasense, a technology made up of genetic snippets that pass through cells and block the expression of some harmful proteins. Wall Street investors learned that when the technology showed signs of failure in a late-phase clinical trial for patients with skin cancer, researchers recruited more research subjects in an attempt to find a statistically significant positive result.

Finally, the available pool of human subjects in the United States is shrinking. The relatively affluent U.S. population is using too many drugs (Gorman 2004). “Treatment saturation” is making Americans increasingly unusable from a drug-testing standpoint, as our pharmaceuticalized bodies produce too many drug-drug interactions, providing less and less capacity to show drug effectiveness and making test results less statistically valid.

Indeed, whatever an American is ready to provide as a human subject, owing to a belief in scientific progress, altruism, or therapeutic need, will never be enough to satisfy the current level of demand for human subjects in commercial science. And that Americans cannot satisfy the need is pushing the human-subjects research imperative to other shores. In this section, I examine historical aspects and operations of North American CROs, members of a specialized industry that began listing and selling securities on public exchanges in the early 1990s and that

focuses on efficient and cost-effective human-subjects research and recruitment.

The demand for human subjects in developing countries is related to the dynamics of industry-sponsored pharmaceutical drug testing in the United States. The roots of an expanding drug-testing regime are traceable to the post–World War II pharmaceutical boom in the United States, when a fee-for-service industry evolved in response to a demand for more safety testing in animals. Another point of origin for the expansion of human-subjects recruitment efforts dates back to the early 1970s, when the use of prisoner subjects in the United States was exposed and severely limited. According to one prominent executive, widely regarded as a founder of the CRO industry, pharmaceutical companies in the United States began internationalizing their human-subjects recruitment efforts as a response to regulatory limitations on prison research. (He directed the internationalization effort for one company in the mid-1970s.)⁷ The scale of U.S. prison research was impressive: An estimated 90 percent of drugs licensed prior to the 1970s were first tested on prison populations (Harkness 1996). When the ban on use of prisoners 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.

By the early to mid-1980s, pharmaceutical companies were routinely outsourcing laboratory and clinical services, including preclinical bioassays, in which the activity of a chemical is assessed (mainly in animal models), and the monitoring of investigational sites and clinical data. By the early 1990s, drug development became a globalized endeavor, in part, under the aegis of the International Conference on Harmonisation, or ICH (in which the U.S. FDA played a key developmental role).⁸ The ICH created international standards for ensuring and assessing the safety and quality of testing procedures for experimental compounds, including Good Clinical Practice guidelines for investigators and the implementation of IRBs. Most importantly, it eased the acceptability and transference of clinical data from foreign investigational sites to the FDA for regulatory approval of new drugs.⁹

Today, CROs are highly competitive transnational businesses that run clinical trials for pharmaceutical, biotechnology, and medical device industries. They offer expertise in submissions of clinical trial data to regulatory bodies and in conducting market analyses of existing and prospective drugs. Their main source of revenue comes from conducting clinical trials in an efficient and cost-effective manner, particularly the second and third phases

of clinical trials, and they are paid to know the constraints and opportunities afforded by country-by-country and regional regulations related to drug testing.¹⁰ CROs are rapidly expanding into the Third World and the former Second World of Eastern Europe, 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.

In selecting a CRO, pharmaceutical sponsors weigh the cost of a study, its quality, and its timeliness. CROs claim to recruit patients quickly and more cheaply than academic medical centers. Most firms are involved in locating research sites, recruiting patients, and in some cases, drawing up the study design and performing analyses. Elements considered in cost-effective trial siting include local levels of unemployment, population disease profiles, morbidity and mortality rates, 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).

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. U.S.-based CROs have alliances with site management organizations in countries in Eastern Europe, Latin America, and the Middle East, for example. Some even have their own centralized IRBs for single-investigator trials or for multicenter trials that can involve studies of up to 10,000 people in 10–20 countries.¹¹ 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). Do clinical researchers have the patient's informed consent? Does the local investigator agree to accept all responsibility in case of an adverse reaction or death? In the international context of drug development, the IRB model avoids the challenge of variability across distinct political and economic contexts. At stake is the construction of an airtight documentary environment ensuring the portability of clinical data

from anywhere in the world to U.S. regulatory settings of drug approval, even if those data were derived in the middle of an epidemic or in a war zone.¹²

Treatment naïveté

This work evolved out of my prior research and writing on the Chernobyl nuclear disaster in the former Soviet Union (Petryna 2002). Working in government-operated research clinics and hospitals in the mid- to late 1990s, I observed a rapid growth of pharmaceutical and clinical trial markets in Ukraine and its neighboring countries. Physicians who tended to Chernobyl sufferers routinely expressed eagerness to learn how to conduct clinical trials and to attract clinical trial contracts from multinational pharmaceutical sponsors because of the abundance of various untreated diseases.¹³ They were also eager because the scientific infrastructures on which they were dependent were quickly deteriorating without state funding. The combination of local public health crises and commercial and scientific interest led to the sudden revaluing of patients who themselves had lost state protection in the form of guaranteed health care. 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).¹⁴ But scientists' rush to reconceptualize their object of study "not as a people but as a population" (Geertz 2001:21) to be brokered as valued research subjects on the pharmaceutical world scene was certainly there.

Currently a turf war is raging among pharmaceutical sponsors for human subjects. The competition is not only about the numbers of subjects a given company can recruit but also about recruiting subjects quickly. 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." CROs see Eastern Europe as a particularly good recruitment site. Given the collapse of basic health care there, patient enrollment in clinical trials is said to be quick. Postsocialist health care systems are conducive to running efficient trials because they remain centralized. High literacy rates in this region mean that subjects offer more "meaningful" informed consent, thus, smoothing potential regulatory problems in the future. Large Latin American cities such as Lima and São Paulo are also considered premium 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 500 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 extent of so-called treatment naïveté—or the widespread absence of treatment for common and uncommon diseases—and treatment-naïve populations are considered "incredibly valuable" because they do not have any background medication (i.e., medications in a patient's body at the time of a trial), or any medication, for that matter, that might confuse the results of the trial. CROs make themselves competitive by locating the treatment naïve. 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."¹⁵

On the one hand, pharmaceutical markets are growing. 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 demographic health transition but whose lives are now shorter, more chronically diseased, and less socially protected.¹⁶ The public health 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 because in these regions clinical trials have become social goods in themselves. And they may well be, providing health care where there is none (Reynolds Whyte et al. *in press*) and medical relief for participants' specific ailments for the duration of the trial.

Although industry and U.S. regulators would not dare codify such justifications for promoting clinical trials in poor areas, in many ways such justifications have already become an industry norm. Yet the question of precisely what made the move of the human-subjects research enterprise to resource-poor settings both ethical and opportune remains unaddressed. In the next section, I consider some key moments in the recent ethical and regulatory discussion of globalizing research in contexts of crisis, which have implications for how experimental groups are being defined and pursued globally today.

Ethical variability: Constructing global subjects

The controversy over placebo use in Africa in 1994 during 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 (Angell 1988, 1997, 2000; Bayer 1998; Botbol-Baum 2000; Crouch and Arras 1998; de Zulueta 2001; Lurie and Wolfe 1998, 2000). Here I consider it as a watershed of another kind: for understanding how a cost-effective consolidation of variability in ethical standards overtook efforts to make a universal ethics (as codified in key ethical guidelines for human-subjects research) applicable and enforceable worldwide. Underpinning this process is a more general anthropological problematic of how new subject populations are forged at the intersection of regulatory deliberation, corporate interests, and crises (upon crises) of health. My specific inquiry here centers on how the ability of the pharmaceutical industry to recruit global treatment-naïve subjects was solidified.

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.¹⁷ 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 experiment, in which low-income communities provide standing reserves of exploitable research subjects. Harold Varmus of the U.S. National Institutes of Health and David Satcher of the U.S. Centers for Disease Control, which, among other government institutions, authorized and funded the trial, claimed the trial was ethically sound (Varmus and Satcher 1996). They cited local cultural variables and deteriorated health infrastructures as 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, is unresolved. Yet these catch phrases represent current responses to the ethics of the trial. The first position builds on well-known cases of marginalized communities acting as human subjects, and those cases, as medical historian Harry Marks (2002) suggests, may obscure more than they reveal about the contexts of experimental communities today. 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. For me, the fact of the African trial—and of the ethical debates that

followed it—highlights the role of crisis in the consideration of differences in ethical standards in the area of human research; indeed, that crisis conditions legitimate variability in ethical standards. Historically, some crises have led perhaps inescapably to experimentation (Petryna 2002; Smith 1990). But one can also ask, are crises states of 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 dimensions of human biomedical research, furnishing guidelines for conduct in research involving human subjects.¹⁸ 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” (World Medical Association 2000:3044).¹⁹ Although the ethics was unambiguous, the regulatory weight of the declaration was not. In this latter domain the winners and losers of the placebo debate would be named.²⁰ 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 and were finding ways to continue using the placebo.

Haziness brought clarification of the rules of the game. Dr. Robert Temple, associate director of medical policy of the Center for Drug Evaluation of the U.S. FDA, undercut the regulatory significance of the declaration and threw his support behind placebo advocates. He stated, “We’ll have to see if the Declaration of Helsinki remains the ethical standard for the world” (Vastag 2000:2983). He cites the ICH (U.S. Food and Drug Administration 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 judgement, 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. Let me briefly trace the logic of this relation. 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 superiority of the new drug to the active control or to at least show difference. (To many patients and clinicians, this is the information of greatest relevance, namely, the comparative effectiveness of a new drug to a standard therapy.) But showing difference or superiority is not enough because “many kinds of study defects decrease the likelihood of showing a difference between treatments” (Temple 2002:222) and make data on difference less reliable. Study defects arise from external factors like poor patient compliance, poor diagnostic criteria, and the use of concomitant medication that can obscure effect. Other defects can include inconsistencies in the application of the 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 be “fatal to a trial designed to show a difference” (Temple 2002:222; also see Pocock 2002:244–245). They 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.

A certain kind of global human subject is at stake in Temple’s description of failure of active-control trials. Most people in low-income countries, those places where many clinical trials are heading, are subject to the external factors that are said to lead to the study defects cited above. They may have medical histories that are patchy at best, thus making cross-cultural interpretation of the meaning of drug effectiveness less reliable. Their diagnoses can be inconsistent, also confusing evidence on drug effectiveness. Not only is quality of data in doubt with active-control trials but also the “quality” of research subjects. Researchers must standardize medical histories if they are to ensure their comparability—time-consuming, costly, and all but impossible tasks.

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. Precisely because they are often poor, without a treatment history, and without treatment, the treatment naïve are the more foolproof and valuable research subjects!

Ethics as a workable document

In responding to the Helsinki declaration revision, U.S. regulators conveyed the value of research efficiency to industrial clinical researchers. And the murky ethics of the placebo could be bypassed by providing for what is known as “equivalent medication”—not necessarily the best or standard treatment, but whatever is available as the best local equivalent. “Do I give them a sugar pill or vitamin C?” as one researcher cynically asked me. In the meantime, the study will be ethical, the data will have integrity, and sadly, the patients will remain treatment naïve.

Another researcher echoed the reality of this shift from concerns about redistribution 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,” he said. In the name of efficiency, pharmaceutical companies and CROs intensified their search for treatment-naïve populations worldwide.

In tracing the relation between regulation and the making of ethics in human research, 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). The main point of this Helsinki genealogy is to show how connected those universes are. 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 story told here is about how regulatory decision making at the transnational level encourages the evolution of “local” experimental terrains whose ethics are workable and whose subjects can be (justifiably) variably protected under current international ethical codes such as the Helsinki declaration. I say “variably” because some national governments faced with a sudden growth of human-subjects research, indeed, have minimal bureaucracies to cope with, and some may know little about, structures of liability in cases of adverse or catastrophic events.²¹ Neither might they have the bargaining power or be interested in pressing for fairer procedures and access to drugs during and after the trial. Thus, a distinction is 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 is balanced against economic, scientific, and regulatory constraints and demands). Ethical regulation entails minimally enforceable procedures governing 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.

The ethical arrangements that have grown up around populations and their diseases are made visible by examining the spatial and temporal complexities associated with global pharmaceutical development and by analyzing the practices of CROs, for example, that fill this demand.

Starting in the early 1990s, just four years before the controversial AZT trials, the FDA began to actively promote the globalization of clinical trials, declaring “that the search for sites and sources of data are part of its mandate to determine the safety and efficacy” (Office of Inspector General, Department of Health and Human Services 2001:42) through the establishment of the ICH. Participation in U.S.-sponsored research began to swell among clinical investigators 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 (in 1995, 4,000; in 1999, 400,000; these are only partial estimates; see Office of Inspector General, Department of Health and Human Services 2001).²²

This global growth of research brought with it a new set of unknowns related to the circumstances of research and concerns about possible exploitation of foreign subjects, and currently, no U.S. legislation or transnational regulatory policy is aimed at controlling or monitoring the conduct of globalizing clinical trials. Many proposals have been made for improving the system of monitoring. In 1999, the Office of Inspector General (OIG), 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.²³ The inspector general’s office recommended that the FDA support and in some cases help to construct local ethical review boards.

The regulatory preference for the expansion of the IRB model was reflected in a recent National Bioethics Advisory Commission (2000) report recommending that studies submitted to the FDA receive ethical committee review both in the United States and in the country in which research is being carried out (as opposed to the present situation, in which only foreign ethical review and approval is mandated). The report supported the idea of dual review but stated that, if host countries have working ethical review committees, then only approval of those committees is required.

These approaches involve monitoring, data collection, and more local ethics committees and lean heavily toward what Iris Young (2004) calls the “liability model” of accountability: Let regulators name the responsible local parties (in some cases, set them up first) and surely those parties can gather information and make the right

decisions, surely they can stop inappropriate research from taking place. Much is also assumed about who is and is not the agent of abuse, most typically defined as the individual investigator him- or herself.

What about instances in which risks present themselves in a more structural form? These instances tend not to find proper nouns in ethical discussions, beyond designation as “interesting” or “scandalous” cases. The fact is that certain conditions have to be met for liability to work: States themselves need to act as protectors and not abusers; transnational corporations need to respect the rights and dignity of all research subjects and recognize that different situations elicit different kinds of coercion; and international ethics codes must be enforceable in cases of clear violation.

None of this occurred, unfortunately, in the following instance—a 1996 case of industry-sponsored research in Nigeria for a drug manufactured by Pfizer, Inc., called Trovan, once one of the most widely prescribed antibiotics in the United States but later taken off the market because it was found to produce serious liver side effects. In an effort to gain FDA approval for a new use of Trovan—this time using pediatric victims of bacterial meningitis who were most likely treatment naïve—a team of Pfizer researchers traveled to the city of Kano during a bacterial meningitis outbreak (which they found out about on the Internet) and civil unrest under the Abacha military dictatorship. Doctors without Borders was already distributing a cheaper antibiotic, proven effective for treating bacterial meningitis, at a main local hospital.

The trial protocol for testing 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. Legal documents show that informed consent forms used in Pfizer’s defense are backdated.²⁴ The Pfizer team went to the hospital where the cheaper drug was being distributed and selected 100 children who were waiting in line to receive treatment. The Pfizer team is alleged not to have explained the experimental nature of Trovan to subjects; parents believed their children were receiving a proven treatment.²⁵ Some of these children were given Trovan in a form never tested on humans before; others were given a lower dose of the standard of care for meningitis (ceftriaxone) that, according to the complaint filed by the New York law firm on behalf of the parents, allowed Pfizer researchers to show that Trovan was more efficacious (Lewin 2001). This low dosing, the parents claim, resulted in the deaths of 11 children.

This is the first case brought by foreign subjects—citizens against a U.S.-based multinational pharmaceutical company. The plaintiffs’ lawyers suggested that a chain of complicity in making the children available for research included Nigeria’s military rulers and state officials, Ministry of Health officials, and local hospital adminis-

trators; U.S. FDA regulators who authorized an unapproved drug’s export to Nigeria for “humanitarian” purposes; and Pfizer researchers who, from a line of children waiting for standard treatments, selected subjects for an industry-sponsored clinical trial. All were involved, lawyers claimed, in violating principles of the Nuremberg Code and other codes of human-subjects protection, referred to in plaintiffs’ court documents as “customary laws” that are “made up of fundamental principles of a civil society that are so widely held that they constitute binding norms on the community of nations” (*Rabi Abdullahi, et al. v. Pfizer Inc.*, Case No. 01 Civ. 8118 WL 31082956 [SDNY 2002]).²⁶

The defendant’s lawyers, by contrast, downplayed the authority of the code and stated that it and other such guidelines “are not treaties.” (In some domestic 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 on as the basis of civil suits in U.S. courts.) The defense situated Pfizer researchers’ activities in the context of a “massive epidemic killing more than 11,000 people,” whose outbreak they attribute to “woefully inadequate” sanitary conditions. By suggesting that their experimental treatment could only do good in such a desperate context, the defense troubled the criteria by which to judge the difference between experimental and standard of care treatment. It stated that it would be “paternalistic” for a U.S. court to adjudicate the appropriate conduct of medical research in a country undergoing a public health crisis, and echoed the ethically relativizing stance already familiar in the African AZT case (*Rabi Abdullahi, et al. v. Pfizer Inc.*, Case No. 01 Civ. 8118 WL 31082956 [SDNY 2002]).

From this brief sketch of the legal parrying, one point is worth stressing. As much as one would like to see the Kano case as an instance of the “dubious” or the “para” (paralegal, pararegulatory, paraethical), an interlocking set of regulatory, commercial, and state interests is at play that can potentially introduce uncertainty with respect to the observability of international ethics codes in local contexts or suspend the relevance of such ethics altogether.²⁷ In this case, a functional ethical review of U.S. industry-sponsored research would have been necessary and might even have prevented this tragedy. But from the Nigerian side of things, interests were not on the side of protection but overwhelmingly on the side of making populations accessible to research.

The case of Trovan is still being adjudicated, but deliberations so far suggest that knowledge of wrongdoing does not necessarily translate into the ability to regulate or prosecute wrongdoers. The case exemplifies how contextual factors (crisis and its humanitarianisms) and defenses fold into and construct new experimental scenarios and groups. Ethical positions, particularly those revealed by the AZT case, that relativize decision making over

appropriate conduct of research to local context inform a legal defense strategy to make acts of experimentation—particularly those enacted in public health crises—either reachable or unreachable by international ethics codes.²⁸ What appears as scandalous activity with respect to global human-subjects research may, in fact, be seen as legitimate under evolving ethical and legal notions of fair play.

This “expedient” experimentality first caught my attention in the context of the scientific management of the Chernobyl nuclear crisis. Here, too, the language of crisis became instrumental, granting legitimacy to experimentation when it otherwise might have had none. A public health disaster combined with the state’s incapacity to protect the life of citizens; this combination, in turn, justified a commercially sponsored clinical trial that would have been impossible to conduct elsewhere at the time. Human research whose exploitativeness might have been hard to judge was justified under the rubric of humanitarianism; and this process in itself may lie outside the bounds of what ethical discourse about human-subjects research and even legal codes can capture.²⁹

Occurring at a time when research priorities in the world of international science were shifting toward biotechnology, Chernobyl afforded a venue for biotechnological research.³⁰ The Soviet state’s response to the crisis is widely documented as having been grossly negligent, particularly in the first days after the disaster.³¹ Under strong pressure to restore the credibility lost by the state’s initial inadequate response to the disaster, then-general secretary Gorbachev agreed to cooperate in an unprecedented Soviet–U.S. scientific venture. He personally invited a team of U.S. oncologists and radiation scientists to conduct experimental bone marrow transplants on workers from the “Zone” (an area 30 kilometers in diameter circumscribing the destroyed nuclear reactor site) whose exposures were beyond the lethal limit and for whom no treatment was available.

In exchange for the credibility garnered from this move, Soviet medical authorities gave in to the U.S. research team’s demands to conduct human testing of a genetically engineered hematopoietic growth factor molecule (rhGM-CSF, thought to regenerate stem cell growth and to be useful for treating leukemia). Some animal testing had been underway in the United States, using highly irradiated chimpanzees and dogs, but human testing of the molecule had not been approved by the FDA. The humanitarian ethics to treat in a crisis where there was no treatment legitimated the transfer and use of unapproved experimental drugs.

The lead scientist on this trial told me that he had no clinical trial protocol but that he had acted consistently “with what was legal.”³² He did not know the exact number of individuals on whom the molecule was tested (he guessed it was over 400). During our 1996 interview, he

described his interests in the Chernobyl cohort as short term. In his view, the accident offered his team a ready-made set of experimental conditions: “The Chernobyl accident for the firemen at the power plant was exactly what we do at the clinic every day. Potentially, there were patients with [leukemic] cancer exposed to acute whole body irradiation.” This scientist, who had gained fame and admiration for his humanitarianism, spoke to me about these unregulated trials in a surprisingly confident fashion, suggesting that political arrangements gave him adequate refuge from ethical sanctions. “No one was going to believe what Gorbachev had to say about Chernobyl. I convinced them of that [in my negotiations]. They had no credibility.”

This scientist’s confidence points to a political, regulatory, legal, and ethical milieu that lay beyond a procedural one governing relations between researchers and their human subjects. Disaster reframed as humanitarian crisis presented a unique scientific and political opportunity. Politically, normal rules of conduct were suspended. Scientifically, the disaster offered a set of negative health circumstances that, because of codes of ethics prohibiting human experimentation, would have been impossible to simulate in normal clinical trial circumstances in the United States.

In other words, the crisis provided a regulatory, environmental, and technical ready-made scenario for bioscientific research. As such, it gave researchers liberal access to a pool of highly endangered people. This pool became attractive precisely when a nonhuman model showing the effects of a particular molecule was lacking. Although the results of this trial were deemed largely unsuccessful, both sides gained significantly from their short-term arrangement. The U.S. scientist’s team and its major pharmaceutical backer got a valuable jump start on the emerging biotechnological market in growth-factor molecules. Soviet officials got a rare opportunity to shore up the state’s credibility locally and internationally.

Biological citizenship

As in both the Trovan and Chernobyl cases, a humanitarian crisis creates a space that appears to be “ethics free” precisely because it is disastrous, beyond the reach of regulation. With the sudden suspension of normalcy, whole groups of people actually or potentially become experimental subjects.³³ Both cases also demonstrate to a greater or lesser extent a breakdown in consent processes and in citizens’ trust and reliance on state systems of public health and protection. Ethics is used variably and tactically by all actors in a chain of interests involved in human-subjects research. Such chains now function in states where lives of citizens are not adequately protected via traditional health or welfare systems. The biological

indicators of whole groups, however formed or damaged by social and economic context, are enfolded into regimes of international and local forms of protection, in which ethics becomes a “workable document.” The issue of human-subjects protection, thus, moves beyond scripted procedural issues of informed consent and into questions of legal capacities and the aggregate human conditions of which they are generative (Marks 2000).

What alternatives are there to counteract perceived widespread abuse and inadequate protection of research subjects? What work is to be done locally, scientifically, and administratively to link biologies back to regimes of protection? In the Chernobyl context, I documented how, in the newly independent Ukrainian state, radiation research clinics and nongovernmental organizations mediated an informal economy of illness and claims to what I refer to as a “biological citizenship”—a massive demand for but selective access to a form of social welfare based on scientific and legal criteria that both acknowledge injury and compensate for it. Such struggles over a biological citizenship took place in a context of fundamental losses (related to employment and state protections against inflation, widespread corruption, and a corrosion of legal and political categories).³⁴ Assaults on health became the coinage through which sufferers staked claims for biomedical resources, social equity, and human rights.

This type of biosocial fabric, in which the very idea of citizenship becomes charged with the superadded burden of survival, is one of many being converted into a model of cost-effective ethical variability in globalized human research. Commercial sponsors argue that clinical trials provide social and material goods to treatment-naïve populations where those goods otherwise might not be available; if these populations do not want the goods, then sponsors can always go somewhere else. “There are so many places that we can work that we just bypass it all together,” one CRO executive told me. In other words, sponsors are free to bargain down the price and “work the ethics” (in terms of equivalent medications) of any trial.³⁵

The circulation of such experimental goods and the relative absence of public scandal over how they circulate do not make the task of gathering more information on the sites and sources of clinical research data any less urgent—particularly in a moment when the FDA actively promotes the “search for sites and sources of data” around the world to fulfill its “mandate to determine the safety and efficacy” of new drugs (Office of Inspector General, Department of Health and Human Services 2001:42). 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 whether anonymity

of the sources of clinical research data is a defensible idea anymore.

Conclusion

In this article, I have sketched an ethnographic approach to human-subjects research—examining its practices and strategies across a variety of international, state, and economic spheres—in the context of an emerging industry of human-subjects research. The overriding empirical problem centers on the apparent ease of access to new treatment-poor populations. In the pharmaceutical pursuit of these new global subjects, one can observe how deliberations over the ethics of research in crisis-ridden areas are set against—even eclipsed by—the market ethics of industry scientists and regulators. Rather than evening the starting conditions in which global human-subjects research is conducted, ethics as ethical variability itself becomes the industry norm, even consciously deployed in pharmaceutical development. Ethics should protect people from harm. Case-based observation and analysis suggest that the procedural issues that are relied on in realizing human-subjects protection are insulating researchers from the contexts of inequality in which they work.

In contrast, current bioethical commentary on the movement of human trials to developing countries centers on the need to produce better ways of deriving informed consent from human subjects and exporting the IRB model at a quicker pace. The purpose here is to ensure that the autonomy of individuals takes precedence over the demands of science or the interests of society, with the idea that such autonomy can counteract coerciveness in research wherever it takes place. An exclusive focus on informed consent narrows one’s vision of what is, in reality, a broad array of factors that are overwhelming ethics. What one is not seeing as a result of the incursion of procedural norms (at least, not yet) is the exercise of free will by autonomous agents in human research. Rather, population-wide processes that support reification (and, in some cases, capitalization) of social and biological difference continue to operate.

This ethnographic assessment of the human-subjects research industry brings into focus emergent ethical arrangements around disease and populations where public health resources have dropped off and where the creation of new poverty is a chronic process. Rather than focusing on normative theory of ethics and ideal conditions, I maintain the importance of apprehending the norms that are being propagated and how they are being refashioned in actual and diverse conditions. Understanding the existing variability in the regulation of ethics and the coinages through which consent, autonomy, and drug markets evolve helps build an ethnographic context that

may ultimately provide the basis for a critique of market-driven human research.

Notes

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1. Source: Business Communication Co., Inc. 2003. This figure is derived from industry surveys, the U.S. General Accounting Office, and the annual reports of seven major philanthropic organizations.

2. According to the Office of Inspector General, Department of Health and Human Services, "Among the countries that have experienced the largest growth in clinical investigators [for U.S. commercially sponsored trials] are Russia and countries in Eastern Europe and Latin America" (2001:i).

3. For earlier warnings on the dangers of ethics becoming disassociated from the empirical realities it claims to know, see Jonas 1969 and Toulmin 1987. Histories of bioethics and medical humanities approaches speak of the loss of intimacy in medical care as codes and norms (related to informed consent, e.g.) transform the patient–doctor relationship so that it is "no longer the intimate affair that it once was" (Rothman 1991:4). Such intimacy, as anthropologists and historians of colonial and post-colonial settings suggest, is rarely a part of medicine in these settings. It is the control of populations, rather than of individuals, that becomes the focal point of medicine in such settings (see Anderson 2003; Arnold 1993; Biehl 2005; Briggs and Mantini-Briggs 2003; Comaroff and Comaroff 1992; Lindenbaum 1978; Misra 2000; Prakash 1999; Scheper-Hughes 1992; Vaughan 1992; among others).

4. Rules and regulations for conducting human-subjects research have been evolving since the establishment of the 1947 Nuremberg Code. The World Medical Association's Declaration of Helsinki states ethical principles that should guide investigators and participants in medical research. The U.S. Food and Drug Administration (FDA) and other government and professional organizations also issue guidelines. The Office of Human Research Protection of the Department of Health and Human Services (DHHS) and the Declaration of Helsinki follow the ethical principles outlined in the Belmont Report (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1974). Yet these guidelines only apply to companies and institutions receiving DHHS funding. In the United States as well as in other countries, clinical trials are monitored by institutional review boards (IRBs). The number of commercial IRBs is growing.

5. By "government" of human-subjects research I mean its ethical codes, the mechanisms of its growth, and its regulation. One goal of my research is to understand how wider ethnographic contexts inform the design and operation of clinical trials. Harry Marks's (1997) work is particularly illuminating in showing how ethics was incorporated into the design of the controlled, randomized trial in the United States in the interwar period. Else-

where (Petryna n.d.), I address the many forms and functions that human-subjects research assumes at local and national levels and how the terms of commercialized human-subjects research are being challenged so as to redirect economic, moral, and scientific investments in particular contexts.

6. 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). One industry contact, however, believes that number is too high. He noted that estimating the number of clinical trials worldwide is next to impossible because there is no central repository. Instead, this individual suggests "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 U.S.—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 and that requires ethnographic attention (Petryna n.d.). Estimating the number of clinical trials is an inexact science, to say the least. Dickersin and Rennie 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" (2003:516). I thank Nicole Luce-Rizzo for her insights and generous research assistance here and elsewhere.

7. I interviewed this individual in June 2003.

8. The full name of this initiative is the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

9. Testing requirements are typically established by national regulatory agencies, and they can differ from country to country; duplicate testing threatened to delay foreign market access and affect the global trade in pharmaceuticals. Japan, perceived to be a potential and large consumer market for U.S. pharmaceuticals, is famous for its intransigent regulatory system. See Applbaum in press.

10. Drug development is broken down into four phases (pre-clinical, clinical, marketing, and postmarketing). Forty billion of the estimated \$55 billion that is being invested in drug research and development goes to development. According to the CEO of one major contract research organization that I interviewed, "Probably 60 percent of that \$40 billion is spent on phase two and three trials. So big money is there." Hundreds of CROs operate worldwide and employ a labor force of nearly 100,000 professionals (Rettig 2000). The move toward outsourcing increased dramatically in the 1990s. By 2004, nearly 42 percent of all pharmaceutical drug development expenditures had been committed to outsourcing; that compared with only four percent in the early 1990s. The pharmaceutical industry is outsourcing an increasing number of operations, ranging from discovery research to clinical trials operations to manufacturing, final packaging, and distribution as well as sales and marketing activities.

11. For an assessment of the commercialization of ethical review boards, see Lemmens and Freedman 2000.

12. See Jonathan Moreno's (2004) analysis of the ethics of human experiments for national security purposes. The focus on standards of consent in a time of international crisis can be read as a means through which a "postwar national security state protect[s] itself from critics of expanded governmental power" (Moreno 2004:198).

13. Post-Soviet scientists were new to the randomization aspect of modern controlled clinical trials.

14. 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" (2001:21).

15. This short genealogy points out some reasons why subjects in health resources-poor areas became desirable for recruitment. Not only are these subjects "desperate" and willing to participate more readily in trials (Rothman 2000) but they also fit a regulatory framework backed by a particular vision of appropriate scientific evidence promulgated by the FDA.

16. *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).

17. 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.

18. The Declaration of Helsinki has been modified five times since its first edition in 1964.

19. This statement, of course, does not pertain to instances in which risk from withholding a proven therapy is lacking, as, for example, in the case of analgesics and antihistamines.

20. At stake in the placebo debate was something more than the issue of standard of care and the global patients' right of access to it. The regulatory weight of the Helsinki declaration, the ability of IRBs to enforce proper research conduct globally, and the definition of just redistribution (particularly in resource-poor areas of the world) remained unaddressed.

21. 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."

22. These numbers refer 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. These countries and others experiencing growth have seen political upheavals during democratic transition and are currently competing to consolidate their "clinical trials markets" in a neoliberalizing context. 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 EU Clinical Trials Directive for EU countries and accession states.

23. 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, Department of Health and Human Services n.d.]

24. I am grateful to Elaine Kusel for providing relevant legal documents, and to Michael Oldani for referring me to this case.

25. Pfizer contracted a CRO, European based at the time, to organize the transfer of blood samples to its laboratory in Geneva to conduct assays on children's spinal fluid samples. 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.

26. The Nuremberg Code was established as a response to Nazi medical experiments on prisoners in concentration camps. The code instituted norms of protection for subjects of scientific research experiments in the form of informed and voluntary consent and human rights guarantees.

27. In another instance of lawyers attempting to eliminate ethical limitations, rather than to assert them, see Alden 2004.

28. The domain of international law in remunerating human-subjects violations is beyond the scope of this article. This problematic has been outlined in Das's (1995) consideration of the Bhopal Union Carbide case.

29. The literature and practice on human rights versus humanitarianism has highlighted this state of affairs over the past decade (see, e.g., Ignatieff 2001 and Rieff 2003). Also see Rabinow 2003.

30. For evidence of the view of Chernobyl as a kind of "experiment" allowing scientists to corroborate or refute biomedical data concerning the long-term health consequences of nuclear exposure, see Nature 1996:653.

31. Because of government inaction, tens of thousands of people were either knowingly or unknowingly exposed to radioactive iodine-131—which is absorbed rapidly in the thyroid—resulting, among other things, in a sudden and massive onset of thyroid cancers in children and adults as soon as four years later. This result could have been curtailed had the government distributed nonradioactive iodine pills within the first week of the disaster.

32. He said he had approval from the FDA.

33. While the rhGM-CSF trials were taking place in a clinic in Moscow, in Vienna, delegations of Soviet, European, and U.S. nuclear industry officials met to decide how to portray the scope of the disaster to the world. In their press release, they announced that 31 cleanup workers had died in the course of work in the Zone. As the officials were negotiating over this number, hundreds of thousands of workers were being sent into the Zone in a massive, ongoing effort to contain the flames and radioactivity of a burning reactor. Humanitarianism in the form of scientific cooperation provided the Soviet state some protection in organizing this massive labor recruitment. The numbers of deaths are not known because of lax monitoring and medical follow-up (Petryna 2002).

34. Social protections include cash subsidies, family allowances, free medical care and education, and pension benefits for sufferers and the disabled. Affected persons, legally designated as *poterpili* (sufferers), number 3.5 million and constitute a full seven percent of the Ukrainian population.

35. In the language of bargaining theory, individual threat points vary globally. A threat point is the level of well-being that could be achieved if bargaining fails. Thanks to Joe Harrington for clarifying this point. Once again, variability seems to be the norm, rather than the exception, as access to clinical trial subjects in contexts of minimal or no care becomes easier. And this variability includes a biological component because in some environments states can no longer protect the lives of their citizens.

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