*BioSocieties* (2007), **2**, 21–40 © London School of Economics and Political Science
doi:10.1017/S1745855207005030

# Clinical Trials Offshored: On Private Sector Science and Public Health

**Adriana Petryna**
Department of Anthropology, University of Pennsylvania, University Museum 334, PA 19104, USA
E-mail: petryna@sas.upenn.edu

**Abstract**
*This article addresses the offshoring of clinical trials to middle- and low-income countries, and the complicated ways in which they have become integral to public health and quality of care in these contexts. I focus on the operations of United States-based contract research organizations (CROs), which make up a specialized global industry focusing on the recruitment of human subjects and investigators; they are key players in an outsourced world of clinical development 'service providers'. To get an on-the-ground understanding of the offshored clinical trial, I worked with regulators, health services administrators, and research clinicians in Eastern Europe and Latin America, two clinical trial market 'growth regions'. By addressing the strategies of evidence-making that inform clinical trial offshoring, this article identifies the context-specific calculations by which experimental groups are being identified. It also addresses aspects of the clinical trial operational model, in which the failure to predict safety outcomes or a paradigm of expected failure is being exported along with the offshored trial. By highlighting the uncertainties of clinical research, this article points to gaps in systems of human protection as it considers new forms of accountability in private sector science and public health.*

**Keywords** global pharmaceuticals, clinical trial environments, offshoring, ethical variability, human subjects, research ethics

## Clinical trial environments

Currently, an estimated 50,000 clinical trials are being run worldwide.[1] Over 40 percent of these new studies are taking place in so-called nontraditional research areas—countries that

**Adriana Petryna** is an associate professor of anthropology at the University of Pennsylvania. She is author of *Life exposed: Biological citizens after Chernobyl* and a coeditor of *Global pharmaceuticals: Ethics, markets, practices*.

1 This work draws from a larger book project, *The human subjects research enterprise* (Princeton UP, forthcoming). Estimates of the current number of clinical trials differ dramatically. The 50,000 number comes from the Boston-based Thomson CenterWatch, which provides intelligence services to the drug industry. To arrive at 50,000, researchers used FDA (US Food and Drugs Administration) estimates of the number of trials initiated annually on the basis of US submissions, the number of drugs currently in development and the average length of trials. One CenterWatch research team member told me that 50,000 is a 'guesstimate'—'very conservative', in his words—in part because of the FDA drug reviewers' lack of knowledge of the number of experiments informing a new drug application. Ambiguity in numerical estimates suggests a global field

are experiencing epidemiological change associated with declining health resources but that have little share in the world's pharmaceutical market.[2] The bulk of these trials are commercially sponsored, and they range from gene therapy studies for rare diseases to studies for treatments for more common disorders; from studies of compounds mimicking existing drugs to studies in search of secondary uses for them.

Poland, for example, registers an average of 400 new trials annually and the neighboring Czech Republic 300. Both countries are now centers of industry-sponsored clinical trials. Most of these trials are phase III trials; they require large and diverse populations and are carried out before a drug is launched onto the market. Dr Renata Novak, a businesswoman managing clinical trials in the Czech Republic for a North American company told me that since that country has one of the highest rates of colon cancer in the world, it has become a hub for colon cancer studies. In most cases, data from such trials will be used to gain approval from the US Food and Drug Administration (or FDA) or the European Agency for the Evaluation of Medicinal Products (EMEA). People outside major drug markets enroll in these trials to access state-of-the-art technology and care. Dr Novak estimated that, so far, one in 100 Czechs (or 100,000 people) have participated in clinical trials, which are now, in her words, 'a normal part of health-care delivery'.

In another example, Poland, which until recently had one of the highest rates of cardiovascular-related death in the world, has developed impressive preventive apparatuses to reverse this trend. The country's leading heart institutes and public hospitals have become preferred destinations for trials of therapies ranging from hypertension treatments to invasive surgical procedures. Hospital administrators so welcomed these trials that, by the late 1990s, the National Institute of Cardiology in Warsaw was 'awash in thrombolytics', or clot-busting drugs, according to one businessman coordinating trials in Poland. He told me, 'Not a single ampule was purchased because each patient who needed that treatment got it from a clinical trial.'

This article addresses the offshoring of clinical trials to middle- and low-income countries and the complicated ways in which they have become integral to public health and quality of care in these contexts. Clinical trials are social institutions, and the question of whether to carry them out, where and how is a political one. These politics bear the stamp of a patterned set of practices inherent to the pharmaceutical industry as it has evolved in North America and elsewhere—I specifically have in mind the history of research among minorities and so-called cooperative patients and professional guinea pigs, and the power the industry exerts over evidence-making and drug regulatory policy.[3]

of experimental activity whose true scope is largely unknown. 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).

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 10. 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 experienced the largest growth in clinical investigators [for commercially sponsored trials] are Russia and countries in Eastern Europe and Latin America' (2001: i).

3 For critiques of the United States system for developing, testing, and using prescription drugs, see Abramson (2004), Angell (2005), Avorn (2004), Goozner (2004), Kassirer (2004); Moynihan and Cassels (2005).

Since 2002, I have been charting the corporate-sponsored clinical research infrastructures in which scientists, regulators, physicians and patients come together. I analyze US-based contract research organizations (CROs), which make up a specialized global industry focusing on the recruitment of human subjects and investigators and on clinical research. They are crucial players in an expanding business world of outsourced clinical development 'service providers'. This world includes everything from patient recruitment firms to investigative sites, investigative site management organizations, academic research organizations, patient data mining companies, data-capture software vendors and commercialized institutional review boards (IRBs).

Several of the largest of these CROs are located in the northeastern United States pharmaceutical corridor. Pharmaceutical and start-up biotechnology companies often rely on CROs to implement and manage global clinical trials according to a given research protocol. In coordinating clinical trials in the United States and abroad, they provide guidance through complex regulatory and legal environments and data management and statistical services. CROs also supply on-the-ground monitoring services to assure their pharmaceutical clients and regulators that clinical research was conducted according to accepted technical standards; that it complies with national and international ethical guidelines concerning biomedical research in humans; and that the data has integrity and is free from fraud. I have interviewed business executives, researchers and clinical trials staff involved in CRO operations in the United States and abroad; as well as collected the professional histories of former regulatory officials and other key players in the pharmaceutical industry. In doing so, I have produced a recent history of the 'clinical trials industry', tracing it back to the post-war boom in pharmaceutical production and to regulatory and health-care system changes in the United States. I also inquired into the clinical trial industry's organization: its scientific expertise, how it responds to evolving regulatory and scientific demands, and the means through which it operates and moves to other countries (otherwise known as offshoring).

The new clinical trial environments that CROs help to tailor are adaptable, mobile and, to some extent, parasitic. They insert themselves in ongoing and unresolved conflicts over market reforms and the role of public institutions in local societies. At any given moment they can move somewhere else. National health and regulatory experts have high stakes in attracting clinical trial investments to their countries and keeping them there. These experts play a key role in shaping the public's understanding of clinical trials—their benefit to patients and to public health systems more generally. To get an on-the-ground understanding of the offshoring of clinical trials, I carried out a comparative ethnographic inquiry in two of the fastest growing regions for clinical trials (Latin America and Eastern Europe), working with trial coordinators, study monitors and local investigators in these regions and where, to some extent, clinical research plays an increasingly important (though generally under-acknowledged) role in public health services provisioning.[4]

4 According to CenterWatch, an investigator is:

> A medical professional, usually a physician but may also be a nurse, pharmacist or other health care professional, under whose direction an investigational drug is administered or dispensed. A principal investigator is responsible for the overall conduct of the clinical trial at his/her site.

A study monitor is:

> [a] person employed by the sponsor or CRO who reviews study records to determine that a study is being conducted in accordance with the protocol. A monitor's duties may include, but are not limited to, helping to

In the summers of 2003 and 2004, I interviewed scientists affiliated with the Brazilian drug regulatory body (ANVISA) and academic-turned-industry-sponsored researchers of the Unit of Clinical Research of the University Hospital in a major city in southern Brazil. Also, in summer 2005 I observed the work of the Polish office of a mid-sized CRO (which I will call Pharmexel). This CRO was competing with other CROs for a slice of the Eastern European and Eurasian clinical trial market. I was particularly concerned with how scientific integrity is maintained and insured in these new markets, as well with conveying the ethical reflections and critiques of the diverse scientific actors involved. The former CEO of Pharmexel told me in 2003 that, 'Given the cost of drug development, we don't go to the clinical trial stage unless we have evidence that a drug works.' His main scientific adviser spoke skeptically about the mechanics of this evidence-making process: 'Companies can now pick and choose populations in order to get a most pronounced drug benefit signal as well as a ''no-harm'' signal'.

By addressing the strategies of evidence-making and the legal and ethical precepts that govern commercial clinical trials, I shed light on the context-specific calculations by which experimental groups are being constituted and the value systems that bring doctors and patients into these trials. My long-term engagement with trial practitioners also points to the gaps in current systems of human subjects protection, both international and national, and I specify the kinds of harm that, despite the oversight of institutional review boards and informed consent, are nonetheless being produced.

In the first part of this article, I highlight some of the regulatory, economic and technical reasons underlying the acceleration and offshoring of clinical trials. I discuss key events that recently framed the public debate over medical research in contexts of public health crisis. In 'zones of crisis', protection and safety considerations are weighed against immediate health benefits or the knowledge to be gained. Ethics and method are modified to fit the local context and experimental data required. And this 'ethical variability' becomes a core value and a presumed course of action in the global testing of pharmaceuticals (Petryna, 2005). The globalization of clinical research cannot be understood without knowing what has happened to clinical research in the United States. Much has been said, for example, of the business interests that pervade clinical research and that can lead to an overemphasis on positive research findings (Healy, 2003; Lexchin *et al.,* 2003). In the second part of this article, I address the clinical trial operational model and debates about its inability to gauge drug safety and risk (FDA, 2004). According to many of my informants, safety problems are detected only after-the-fact; and this retrospective detection speaks to a fundamental abandonment of the scientific method to characterize harm. The failure to predict safety outcomes or a 'paradigm of expected failure' is being exported along with the offshored clinical trial model. The CRO perspective allows an appreciation of the persistent problems and uncertainties underlying the clinical research enterprise, and it points to gaps in oversight and responsibility. The operations through which efficacy and safety data happen become ethnographic contexts from which to observe the benefits and risks of private sector science as it is rapidly integrated into public health systems in emerging drug markets.

plan and initiate a study, and assessing the conduct of studies. Monitors work with the clinical research coordinator to check all data and documentation from the study.

Reference: http://www.centerwatch.com/patient/glossary.html#5

## Pharmaceutical capital: contract research in brief

So, what drives the demand for larger pools of human subjects? First, as I mentioned earlier, simply the sheer number of trials being run. The advent of blockbuster drugs with sales of over a billion dollars annually has led to the profitable 'me-too drugs' business. With minimal pharmacological alteration, these drugs build on or mimic blockbuster drugs and are not especially innovative[5]. Second, to satisfy US regulatory demands, increasingly large numbers of patients must be included in clinical trials to prove long-term safety, especially of drugs designed to be widely prescribed. Third, some drug categories—like antihypertensives to control blood pressure and statins to control cholesterol—are expanding dramatically as new compounds are developed. Competition to get drugs approved and marketed steps up the search for subjects. Fourth, there is significant growth in the number of new chemical entities—patents are inundating the United States Patent Office for compounds that have yet to undergo clinical testing (CenterWatch, 2005).

Shifts in the very science of drug development also impact subject recruitment. As new molecules are discovered, more experiments are taking place (before the formal phases of human testing) to determine their clinical and market viability. Also, the available pool of human subjects in major Western pharmaceutical markets is shrinking. 'Treatment saturation' is making Americans and Western Europeans increasingly unusable from a drug-testing standpoint (see Gorman, 2004). As the late Hein Besselaar, the grandfather of the contract research industry, put it to me in an interview in 2004, 'People in the West live on pills. You have the 50-year-old who takes three or four different medications. Someone living in Eastern Europe may be on one medication for high blood pressure or whatever, but certainly not three or four.' In other words, our bodies produce too many drug–drug interactions and are less and less able to show specific drug effectiveness, making test results less statistically significant. Whatever numbers Americans or Western Europeans are ready to provide as human subjects—owing to therapeutic need, belief in medical progress or altruism—it will never be enough to satisfy the current level of demand for subjects in private sector science. And the fact that we can't propels the human subject research enterprise to other shores.

The roots of a specialized contract research regime are traceable to the post-Second World War pharmaceutical expansion, when a fee-for-service industry evolved in response to a demand for more safety testing in animals. In the early 1970s, a few CRO-like consultancies were established as adjuncts to the pharmaceutical labor force. As a former executive explained to me:

> They were a cottage industry, people working out of garages with a few computers-scientists who came out of the industry with experience and said I can take on some of this data management work or trial monitoring on a contract basis. But pharma did not trust these people with anything large or complicated.

By the early 1980s, pharmaceutical companies were regularly outsourcing laboratory and clinical services, including the monitoring of investigational sites and the data produced. Mega-trials and me-too drugs came into vogue, and CROs promised expertise and reduction in time and cost. For example, the founder of one of the largest CROs made his name in the

5 On this point see Angell (2005).

fiercely competitive 'antacid wars' in the 1980s; he led the research program for Zantac, which helped turn Glaxo around after several years of decreasing profits and became the largest-selling drug of its time.[6] This scientist started to manage entire clinical research programs once he left the industry in 1985. As he told me in 2004: 'A company like Ciba-Geigy would come to me and say, ''our track record of doing clinical development is so poor. Our last beta-blocker took ten years from first patient in until FDA approval. You say that you can do it in four years, you've got the contract.'''

By the mid 1990s the research enterprise was booming and many CROs went public. Through 1999, CRO size relative to the demand for contract research services was relatively steady. That steadiness, I was told, was driven by a continual stream of new molecules in the pipeline and 10–12 percent annual increase in R&D spending. The pharma capital to be made was in clinical research. As one industry executive told me in 2003: 'Fifty-five billion dollars go into research and development. Forty billion of that is in development. And of that forty billion probably 60 percent is spent on phase II and III trials. So big money is there'.

Today, the CRO industry claims that it provides for roughly 40 percent of the number of clinical research personnel engaged in drug development activities.[7] Its experts provide guidance through complex (and variable) regulatory environments to determine the time it takes for studies to be approved and launched in different countries and the marketing possibilities there. Most CROs are involved in locating research sites, recruiting patients and, in some cases, drawing up the study design and performing analyses. Sometimes they work directly with primary health-care facilities, hospitals or consortia of therapeutic specialists. Some even have their own centralized ethical review boards.[8]

Clinical trials are divided into four phases. Phase I studies rely on roughly 20–80 healthy volunteers and determine the tolerable dose range of a new drug. Phase II studies evaluate efficacy and safety in 100–300 subjects who have the disease or condition to be treated. Phase III studies generate more safety and efficacy data. They are generally multicentered and can involve up to 10,000 people in 10–20 countries. This phase is the most time-consuming and expensive.[9] Phase IV studies provide further safety and efficacy information after the drug has been marketed, and they can involve millions of people.

This four-phase model of drug development was implemented in the late 1960s, on the heels of the scandal around thalidomide, a sleeping pill also used for morning sickness in pregnant women. Thalidomide was marketed internationally, then, in 1962, reports of infants with incomplete hands or feet sprouting from bodily trunks and their connection with the drug were reported in major medical journals. An estimated 10,000 children in 46 countries were found to have been born with deformities. The thalidomide crisis served as a government wake-up call over lax testing standards in the drug industry, in which new compounds were tested 'on the basis of whatever pharmacologic and toxicologic data seemed sufficient' (Wardell and Lasagna, 1975:16).[10]

6 The drug is used to treat peptic ulcers, gastritis, and esophageal reflux.

7 This estimate is given by the Association for Clinical Research Organizations (http://www.acrohealth.org/trends.php). ACRO is the main lobbying and trade organization for the world's largest CROs.

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

9 When I refer to clinical trials in this article, I am mainly referring to Phase III trials.

10 As Hein Besselaar recounted to me in 2004, 'That was really the situation that set the regulators on their course to make the whole process of drug approval and therefore the regulatory affairs business much more rigid than it

In response to the crisis, the US Congress mandated that the US Food and Drug Administration use randomized trials to evaluate new drugs not only in terms of their safety but also in terms of their efficacy. Randomization is the process of assigning trial subjects to treatment or control groups using an element of chance to reduce bias of selection. This statistical bias-reduction strategy came, in part, from a progressive impulse to limit false beliefs and business interests in medicine (Marks, 1997).

In the context of global trials, this strategy is applied, but it is also circumvented. There is now bias-induction in both the recruitment of epidemiologically convenient populations and in protocol design, as the chief scientific officer of a US-based CRO critically told me:

> In my recruitment strategy, I can use subject inclusion criteria that are so selective that I can 'engineer out' the possibility of adverse events being seen. Or, I can demonstrate that my new drug is better by 'engineering up' a side effect in another drug (by doubling its dose, for example). That is the big game of clinical trials.

This scientific officer heads a 'triage committee' along with two other physicians in his company. Together they review pharmaceutical research protocols and decide which ones they should pursue and bid on. He explained the rationale for such a committee, 'It used to be that, when you are a CRO, you just get handed the study. You really don't understand it, you just do it.' Today is a different story: 'We are seeing many more protocols with subject inclusion and exclusion criteria that are simply too difficult to fulfill … like advanced untreated diabetes.' He and his colleagues avoid bidding on some of these studies 'because it is too dangerous and costly for us to monitor patients … The experiment becomes too difficult to control on the ground.' Indeed, CROs have different standard operating procedures with respect to accepting riskier protocols and potential liabilities. This informant also felt that the bias built into recruitment strategies and protocol design was increasing chances of ineffective and even unsafe drugs gaining FDA approval. In short, and as this professional made clear, the global expansion of clinical trials goes hand in hand with new strategies of demonstration that carry their own forms of risk.

## Constructing global subjects

The expansion of pharmaceutical testing worldwide is not only driven by industry motives. During my field research in the mid to late 1990s on the social and political aftermath of the Chernobyl nuclear disaster, I observed a rapid growth of pharmaceutical markets in Ukraine and its neighboring countries (Petryna, 2002). Some physicians who tended to Chernobyl victims told me how anxious they were to learn how to do trials and to attract clinical trial contracts both because of the abundance of various untreated diseases and because the scientific infrastructures on which the physicians were dependent were quickly deteriorating without new public funding. This mix of ongoing public health crisis and the needs and

was before.' And in the wake of that scandal, there was a dearth of regulatory-minded drug development experts. Besselaar had organized his postgraduate medical studies to fill this vacuum as a contract researcher: 'I learned a lot about how to organize the human phase of drug development, and not the animal phase, and I thought maybe there is a business there.'

interests of local scientific communities was leading to a reconceptualization of patients and their value.

CROs see Eastern Europe as a particularly good recruitment site. Postsocialist healthcare institutions are conducive to running efficient trials because they remain centralized and have a reasonable scientific infrastructure. Given the unmet demand for specialized care, patient enrollment is said to be quick. High literacy rates in these areas mean that subjects offer more 'meaningful' informed consent, thus minimizing potential problems with auditors. Large Latin American cities such as São Paulo are also considered premium sites because, as one recruiter told me, 'Populations are large. It's a question of how many patients I can get within a limited area, which reduces travel cost.'

Some regions and countries are more attractive than others because of the abundance of what is commonly known as 'treatment naïveté', a term that refers to populations that (apparently) have not been diagnosed or treated for a particular condition. Treatment-naïve populations are considered 'incredibly valuable', as one researcher told me, because 'these populations offer a more likely prospect of minimizing the number of variables affecting results'. That people in low-income countries also might be taking several drugs or treatments, often unsystematically, has not deterred companies from identifying particular contexts in those countries as sites in which the 'naïve' might be found, in a poorer region or provincial hospital, for example.[11]

The increasing choice of Third World citizens to be subjects of global drug trials parallels their poverty status. Even if the trend in drug trial expansion can be justified in terms of potential health benefits, pursuing disadvantaged populations that have (as yet) little or no legal recourse in case of harm involves troublesome ethics. The baseline conditions that would make a universal ethics applicable and enforceable worldwide are highly uneven. Critiques of such experimental regimes focus heavily on procedural issues—clinical conduct and informed consent—as if harm could be exclusively located within a traditional model of physician-induced neglect. As efforts are made to expose violations of individual bodily integrity, social scientists also need to chart how people are categorized and gathered into these experimental regimes, and why protective mechanisms are at times unable to intervene. We also need to look at the value patients bring to these regimes and what is owed to them, such as continued treatment once a trial is over.

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.[12] Here I take it as a watershed of a different sort: of how subject populations are generated at the intersection of regulatory deliberation, commercial interest and crises (upon crises) of public health. In this well-known case, some US 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 was

11 On 'irrational' treatment uses, see Etkin (1999). On the circulation of pharmaceuticals within the lifeworlds of the urban poor in Delhi, see Das and Das (2006).

12 For different perspectives on this controversy, see Angell (1988, 1997, 2000), Bayer (1998), Botbol-Baum (2000), Crouch and Arras (1998), de Zulueta (2001), Farmer (2002), Lurie and Wolfe (1998, 2000), Rothman (2000).

available.[13] Critics viewed the use of a placebo arm as highly unethical. Research in developing countries, therefore, was being held to a different standard than in the developed world.[14]

Harold Varmus of the National Institutes of Health (NIH) and David Satcher of the Centers for Disease Control (CDC), which, among other institutions, authorized and funded the AZT trial, claimed that the trial was ethically sound. They cited local cultural variables and deteriorated health services 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 under such stress, and it was within the jurisdiction of local and national authorities to decide on appropriate research conduct and treatment distribution.

Ethical imperialism or ethical relativism? These were the terms of the debate. The first position builds its case on histories of marginalized communities that were coerced or misled into experiments and greatly suffered as a result. Historians point to other communities, such as those of the 'cooperative' patients and professional guinea pigs, that complicate these histories of coercion (Marks, 2002). The second position (ethical relativism) 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 AZT trial and the debates that followed it highlight the role of crisis in the consideration of variability in ethical standards in human research.[15] Some crises have led, perhaps inescapably, to experimentation. But one can 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 one?

13 In the trial business, a placebo is an inactive treatment made to appear like real treatment; it amounts to no treatment.

14 Marcia Angell (2000), for example, said that practices like the use of a placebo arm were reminiscent of the Tuskegee experiment, in which, for decades, African-American men were followed to observe the natural course of their untreated syphilis.

15 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 faulted for an alleged blind defence of local culture. See 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 (1999) 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 (Kim *et al.*, 2003) has exposed the way moral assumptions in health planning can further entrench inequality, justifying some interventions while disallowing others. Other medical anthropologists have shown how the local trajectories of pandemics are influenced by the logic of international policy and choices (Biehl, 2001; Cohen, 1999; Das, 1999). 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 (see Petryna and Kleinman, 2006). These works move beyond an emphasis on difference in the health arena, and point to the kinds of empirical work that are required to address the moral, ethical and cultural realities of emergent global drug markets.

The debate over the ethics of the AZT trial prompted the sixth revision of the Helsinki Declaration, which deals with 'all aspects of human biomedical research and provides guidelines for research involving human subjects'.[16] The 2000 revision stated that placebos should not be used 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.' If the ethics were unambiguous, the regulatory weight of the declaration was not. Pharmaceutical companies, already 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 eager to learn from regulators about the legal enforceability of the declaration while finding ways to continue using the placebo.

Dr Robert Temple, the influential former director of the Center for Drug Evaluation at the FDA, clarified the rules of the global drug development game. He undercut the regulatory significance of the declaration and threw his support behind placebo advocates. He referred to the Guideline for Good Clinical Practice, issued by the International Conference on Harmonization (ICH-E10, 2001) in the early 1990s, as the alternative and more relevant guideline on the ethics of placebo use. This ICH brought together regulatory authorities of Europe, Japan and the United States with industry experts, and it made clinical data from international research sites transferable and acceptable to regulatory bodies in these major markets. 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 *regions and . . . populations chosen*' (Temple, 2002: 213, emphasis added). In other words, the ethical standard for research in the world was variability.

In fact, Dr Temple's backing of the placebo trial was informed by a concern about the integrity of scientific data. The alternative to the placebo control is the active control trial. With active controls—in which a new drug is compared with a standard one—one has to worry about an increased chance of study defects that may invalidate the data, such as poor patient compliance and the use of concomitant medications on the part of the patient that can obscure effect. The treatment-naïve are preferable subjects given this logic. It is precisely because they are often poor and supposedly do not have access to medical treatments that they are considered more foolproof and valuable research subjects.

One researcher I interviewed said the FDA's response to the Helsinki Declaration revision 'made research efficiency a priority and this was in line with what industry wanted'. The murky ethics of placebo use could be circumvented by offering what is known as equivalent medication—not necessarily the best or standard treatment, but whatever is at hand as a best local equivalent. 'Do I give them a sugar pill or vitamin C?' as he cynically asked me. In the meantime, the study will be ethical, the data will have integrity and, sadly (in some cases), the patients will remain treatment-naïve.[17]

16 The Helsinki Declaration has been modified five times since its first edition in 1964. It deals with 'all aspects of human biomedical research, providing guidelines for investigators to follow in research involving human subjects' (Guess *et al*., 2002: 19).

17 Another researcher echoed the sense that concerns have shifted from justice to efficiency-based standards in global research when he told me that ethics is 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 accounting for the link between regulation and the making of ethics in human research, historian Harry Marks writes, '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 AZT trials demonstrates how connected those universes are and how regulatory decision-making at the transnational level encourages the evolution of 'local' and 'ethically variable' experimental terrains.[18]

To attract pharmaceutical investments, the regulatory agencies of many countries soon signed up to the International Conference on Harmonisation (ICH). Signing up meant these countries would begin the costly work of setting up agencies that could standardize and monitor the conduct of trials in their countries. They would also build ethical review boards to ensure the rights and protections of patients. This process was slow, yet the subjects involved in international clinical trials grew from 4,000 in 1995 to 400,000 in 1999. These numbers are low, as they refer to new drug applications (NDA) only.[19] Indeed, they are *very* low, considering the kinds of experimental activities that are not registered and hence not officially accounted for. Some clinical research does not require registration: preclinical and postmarketing studies and studies of new uses for drugs already developed to treat certain conditions (providing the mechanisms of action are similar), for example. Trials leading to rejected drug applications are also not counted by the FDA. Estimating the number of clinical trials globally is an inexact science, and those attempting to do so are faced with a complex global field of experimental activity whose true scope is not known (Sim and Detmer, 2005).

The largest increase in clinical trial participation occurred in Eastern Europe and Latin America. This global growth has brought with it a new set of unknowns over the circumstances of research and concerns over possible exploitation of foreign subjects. In 2001, 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. The Office of the Inspector General recommended that the FDA support and in some cases assist in establishing local ethical review boards.

This approach leans heavily on IRB oversight and toward a liability model of accountability: let's name the responsible local parties (in some cases set them up first), and surely they can gather information and make right decisions, surely they can stop inappropriate research from taking place. A working legal system is assumed. Much is also assumed about who is and isn't the agent of abuse, most typically defined as the medical investigator.

As the rapid and semiregulated growth of clinical trials was under way, scandals arose that exposed the structural flaws and real absences of institutionalized protective structures in a hastily globalized system. Consider the now infamous case of Trovan, a widely prescribed antibiotic that had been taken off the market in the United States because it was found to have serious liver side effects. A 1996 Nigerian trial was supposed to show that Trovan could be used to treat meningitis, but the protocol was not approved by a US ethics

18 A recent review (Kent *et al*., 2004) found that ethical guidelines that specify best proven therapy are routinely being violated, regardless of decisions made by local or international scientists and regardless of funding sources.

19 An NDA is an application to the FDA to obtain a license to market a new drug in the US.

committee and received inadequate review in the host country. Lawyers for Nigerian plaintiffs moved against Pfizer in the deaths of 11 children, who were among the trial participants. The trial happened during a massive outbreak of bacterial meningitis in the context of a civil war. Some children were given Trovan in a form never tested on humans before; others were given a lowered dose of a proven therapy for meningitis (ceftriaxone) that, according to the legal complaint allowed researchers to show that Trovan was more efficacious. The plaintiffs' lawyers claimed that this lower dosing caused the children's deaths. They suggested an array of complicitous interests in making the children accessible for research that includes Nigeria's rulers, Ministry of Health officials, local hospital administrators, FDA regulators who authorized an unapproved drug's export to Nigeria for humanitarian purposes, and company researchers who redirected children waiting for standard treatments to their own experiment.

Even if there had been a functional ethical review of US industry-sponsored research, the tragedy might not have been prevented so long as these interests were not on the side of protection but, overwhelmingly, on the side of making populations accessible for research. Pfizer argued that the case should be adjudicated in Nigerian courts. The Southern District of New York court recently agreed. The families intend to appeal. As this brief sketch of the legal sparring shows, ethical regulation is a realm of contingent practice, and the allocation of protection for human subjects is far from settled.

## The paradigm of expected failure

The demand for human subjects in developing countries cannot be understood without knowing what is happening on the US pharmaceutical scene. One point of origin for a commercial expansion of trials dates back to the early 1970s, when the use of prisoner subjects in the United States was exposed and severely criticized. An estimated 90 percent of drugs licensed during that time were first tested on prison populations (Harkness, 1996). When the ban on the use of prisoners finally set in (for particular phases of testing) in 1980, pharmaceutical companies lost almost their entire base of human volunteers and shifted a good deal of their research elsewhere.

But the continuation of prison research had strong advocates. Dr Louis Lasagna, cofounder of the Tufts Center for the Study of Drug Development, made the case that, in shutting down the US prison-testing infrastructure, researchers were losing the ability to test for adverse reactions to drugs. Prisoners, especially recidivists, made long-term safety studies possible. Referring to the closing of a Kentucky prison-related addiction research center, Lasagna wrote, 'Without such a facility, this work is unlikely to be done elsewhere, and the sick public will become the unwilling (and unconsenting) research subject of the future' (Lasagna, 1977:2351).

What was called liability testing had been foreclosed and remains the most underdeveloped aspect of drug testing. Generally speaking, the public still lacks the means of evaluating the safety of drugs after they are put on the market. This became alarmingly clear in the recent cases of the painkiller Vioxx and antidepressant SSRIs, the latter shown to increase risks of suicidality in children and youth (Healy, 2003). Many industry people link rising drug costs to adverse drug effects and product liability suits. One CRO professional went

further and suggested that current drug development operates on what he called the 'the paradigm of expected failure'. He told me that:

> 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 are spent on going back and fixing the data after the fact.

In this find-and-fix approach, safety problems are detected after the fact and this makes everybody anxious, not just the public but some of my contract research informants as well. The dangerousness of some protocols is typically understated in the original outsourcing contract. Consequently, liability issues too are an after thought. As one American contracts lawyer working for a small pharmaceutical company told me, 'Unfortunately, it takes an injury in clinical trials to figure out who is going to be responsible.' The recent multiple organ dysfunction and catastrophic immune response in six test subjects during an outsourced phase I trial of the monoclonal antibody TGN1412 in England serves as an example.

Arguably, pharmaceutical outsourcing reflects what in economics is known as the theory of incomplete contracts which explains how contracts are structured in situations of uncertainty, leaving room for contingent or opportunistic behaviors and unsolved liabilities.[20] The above mentioned CRO informant was working diligently to improve the outsourcing contract: to minimize contingency, to turn the unwritten terms of responsibility and liability into explicit negotiating items, and to generally produce better informed contracts.

Back to history: by the early 1990s, the bulk of clinical trials still took place in Western nations. The increase in new chemical entities I mentioned earlier produced an over-demand for investigational sites, and US pharmaceutical companies and CROs began to tap and now even prefer medical group practices and primary care centers (over the more typically used academic institutions). Physicians were eager to turn their practices into investigative sites. This interest was a response to lowered reimbursements from the governmental health insurance program (Medicare) and changes in the structure of health insurance payments (related to the rise of health maintenance organizations). The clinical trial economics that were intended to help physicians recoup shrinking profits also created new sources of unease, such as the so-called floater sites. Such sites promise many patients, routinely underbid for contracts and are not particularly concerned with achieving standards of regulatory compliance. They basically make their money and then disappear from the clinical trial food chain. Their existence lowers the profitability of clinical research in the United States.

The proliferation of floater sites has not been matched by an expansion of auditing mechanisms, and there are concerns over the reliability of the data produced at these sites. Some industry actors note that one factor pushing clinical research to other countries is this phenomenon—whether it is the pursuit of more floaters elsewhere or as an escape from the economic constraints the phenomenon imposes here.[21] Countries like Poland, for example, bid their research services as an alternative to floater sites, and as producing more reliable data.

20 I am grateful to Veena Das for pointing me to the theory of incomplete contracts.

21 This point was made publicly by the owner of a small US-owned clinical trials company at an industry-sponsored conference in December 2004.

## Keeping the clinical trial market in Poland

Drug companies invest almost half a billion dollars in clinical research in Poland each year. The medical director of a major pharmaceutical firm operating in Poland told me in 2005 that Central-Eastern Europe is the 'second largest producer of clinical data' after the United States. I followed clinical trials staff and scientists of one CRO to its Warsaw affiliate to see how clinical trial environments are tailored and operationalized. Here it is not a matter of looser standards or circumvention of FDA regulations, but about how such environments are tinkered with to be sustainable and profitable over a long run.

I first met Dr Jan Mazur[22] when he visited the US headquarters of Pharmexel. Mazur leads this mid-sized CRO's clinical trial services strategy and expansion across Central-Eastern Europe. He came to speak to Pharmexel's marketers about the region's high data productivity.

During his presentation, Mazur provided data about his country's dire health predictors and its poorly financed health-care and universal health insurance systems. He juxtaposed this data to information about the high quality of clinical research and Poland's adaptation to international standards.[23] The message to get to potential clients was clear: they will not fail in recruiting and they will have reliable data. Mazur also conveyed clinical trial success stories; they all involved what are known in the industry as 'rescue studies'. The term applies to studies that start in one location and, because of poor recruitment, are moved to another location midway through the trial. So, for example, it takes one year for 50 investigative sites in Western Europe to recruit 200 rheumatoid arthritis patients. Whereas five central-European sites recruit the exact same number in just two months.

When I arrived in Poland, however, Mazur's success stories turned out to be a bit more complicated. One such story involved a placebo-controlled study for a diabetes drug. The study's inclusion criteria required previously untreated (or treatment-naïve) patients with 'very high' blood-sugar levels. In Western Europe, subject recruitment for the study was exceedingly low. And in Poland, Dr Mazur expressed anxiety about pressures to recruit 'dangerously sick patients'. He told me, 'If you are newly diagnosed, you cannot possibly have such high blood-sugar levels!' He was referring to 'normal' medical contexts, where diabetics would be diagnosed and treated at much lower blood sugar levels. He seemed to suggest that timing of diagnosis was everything. There was room to maneuver and therein lie potential abuses.

Dr Mazur explained to me that the study drug was not significantly different from what was already on the market, but the patients were chosen in a way that made small therapeutic differences more obvious (it was a me-too). He was able to slightly modify the inclusion criteria to recruit patients with a slightly less severe condition—in his words, to make 'non-existent patients' come into existence. Because of the 'complexity' of this protocol, the CRO also hired its own on-site physicians to review each and every patient already randomized—to make sure they are actually *eligible* for the trial.[24] 'It becomes very difficult to exclude

22 This is a pseudonym.

23 Quality was measured by Poland's low 'finding per FDA inspections ratio'.

24 Complexity is reflected in the number of different subject inclusion and exclusion criteria, I was told,

> The patient has to be like that, but can't be like that; he has to meet certain parameters and have certain symptoms.… Sometimes the patients are non-existent. Pharma companies want to prove something for

other causes for the same symptoms and signs, and the wrong people may get into the trial. It's a safety issue.' Dr Mazur was extremely conscientious, and his company valued him for it. But I could not help but wonder what others in the same position may or may not choose to do.

The 'complex' studies Dr Mazur spoke of were predominantly rescue studies for me-too drugs. These were not gene therapy or cardiac intervention trials—trials that we might normally associate with more complexity—but trials for drugs that constitute the majority of the drugs that are FDA approved today (Angell, 2006). Taming complexity seemed to be an unwelcome part of his expertise, but one he had to deploy, lest he jeopardize Poland's privileged position in the clinical trials global market. But who is responsible for the danger in the me-too protocol? The drug manufacturer always had the option of taking the protocol elsewhere—to another CRO, to another country—if Pharmexel decided to reject it. The company's added efforts to make protocols do-able and safe (by hiring their own physicians, for example) were driving up their costs.

Hidden harms—sometimes, there is no rescue from them. Consider the recent troubles with rofecoxib (Vioxx) a drug that belongs to a class of drugs that is now known to increase the risk of heart attacks. A meta-analysis of rofecoxib trials that appeared in *The Lancet* revealed that evidence of cardiovascular risk from the drug was known before September 2004, when Merck withdrew the drug from the market (Juni *et al*., 2004). The drug maker offshored clinical research to Eastern Europe in the mid 1990s, before able study monitors like Dr Mazur arrived *en masse* on this up-and-coming clinical trial scene. Vioxx underwent testing in countries such as Poland, which, as I mentioned, have seen some of the highest rates of cardiovascular-related deaths in the world. *The Lancet* article suggests that contexts with different background risks can lead to a misclassification or underappreciation of coronary events, which, in turn, 'could have biased results in trials that did not include external appraisal of safety outcomes' (the use of monitors, for example).[25]

I spoke to several Polish and Russian investigators who ran Vioxx studies and they, understandably perhaps, denied any problem at their sites. But, for Dr Mazur, the protocol itself carries background risk. He said companies can choose the most cost-effective tools to observe and record patients' symptoms (for instance, using cheaper pain-scales rather than more expensive laboratory exams to verify drug-related symptoms or effects). But this is not a matter of simply saving on costs. His colleague in the United States went further and told me that, 'adverse events are not just inadequately reported, but harm in general is under-hypothesized'. Its acknowledgement may be deferred or in his words, simply 'engineered out'. And, if harms are revealed (in the post-marketing stage, for example), they can be attributed to environmental or individual causes rather than to the study drug.[26]

non-existing patients. I don't know why. But I think they are driven by trends in the pharmaceutical market, by competition to prove . . . that one medication is better than others.

As his director put it: 'The industry is pushing towards this selectivity in order to maximize signs of drug benefit. As a result, the experiment is too difficult to control on the ground.'

25 The quote continues: 'the inclusion of an independent endpoints committee should be the rule, and exceptions to this rule should be justified (2004:2025).'

26 Indeed, the notion that adversities stemming from the drug can be *obscured* by 'normal' background risks in a given context was precisely the argument the FDA used to explain why it failed to flag Vioxx as risky: 'The national adverse event reporting system that helps the FDA flag dangerous side effects was of little use in this

## 'Pharmaceuticals are the new gold'

There are also socio-economic harms at stake in globalized clinical testing. For the past three summers, I worked with academic researchers in the newly built Unit of Clinical Research of the University Hospital in a major city in southern Brazil. The team, led by Dr Paulo Picon, was critical of the ways pharmaceutical companies and CROs were influencing the course of medical research and public health in Brazil. Dr Picon and his team were analyzing the efficacy and dosage requirements of new drugs entering the market. They were particularly concerned with drugs that do not promise to cure or extend life, but simply lower some non-clinical indicator, such as the reduced virological response promised by the hepatitis C drug, peginterferon. Some new drugs cost 20 times more than existing treatments, and these researchers are showing that their efficacy is not much better. 'The industry is pressuring the state to purchase these drugs,' Dr Picon said, and he added: 'Pharmaceuticals are the new gold.' He went on to compare a gram of peginterferon to a gram of gold:

> One gram of gold costs 50 reais, $24. Today, one gram of peginterferon costs 4.4 million reais 2 million dollars ... one gram. With this one gram you can treat 110 patients and you might prevent, you *might* prevent one liver cirrhosis. One cirrhosis in 110 patients ... you *might* prevent.

Desperate patients demand these treatments, as the country's constitution guarantees the right to universal health care. They are modeling their efforts after successful movements by AIDS patients in Brazil and the United States (Biehl, 2006; Epstein, 1996).[27] Today, this combination of patient activism and commercial science is leading to what anthropologist Joao Biehl (2006) calls a 'pharmaceuticalization of public health', raising vital questions about public health priorities, financing and equity. These university researchers are creating a kind of counter-science, designing protocols that show that lower doses of certain drugs are equally efficacious and cost less. They are also working with local prosecutors and educating judges to make sure that this alternative evidence will have some legal weight.

In September 2005, a group of clinicians active in industry-sponsored research and working in another hospital, told me of a problem they are currently facing. They were conducting a clinical trial to test the efficacy of a new therapy for a rare genetic disorder. Advanced-stage patients who had never received any treatment were recruited, according to the study's strict inclusion criteria.

The well-respected director of the genetics service was eager to secure the contract for the trial because of the resources it would bring to the service. Without his colleagues' knowledge, he agreed to the sponsoring company's demand to reserve the right to withdraw the drug at any time—this was written into the consent forms that the patients signed. Informally, however, the company agreed to provide medication for two years, and it continued

case because the ailments possibly caused by Vioxx—heart attacks and strokes—are so common' (Masters and Kaufman, 2004: A01).

27 Indeed, there has been a shift since the 1980s with the integration of desperate patients suffering from cancer and AIDS into 'fast-track' research. Acknowledging this group of special patients called for flexibility within medical institutions with regard to the process of evaluating the effectiveness of therapies through clinical trials. In terms of drug access Brazil's free dispensation of combined anti-retroviral treatments has been hailed as a model of AIDS intervention in a low-income country.

to do so for a third year. The drug worked well. But, without notice, the company pulled the study drug. A company representative hinted to the clinicians that Brazil was too slow in registering the drug. Company lawyers had contacted the patients to spur a patient activist group to pressure the government to buy these drugs (which can cost up to $200,000 per patient annually). This effort failed. Later, I learned that the company running the trial had been sold. Whatever had led to the withdrawal, the clinicians involved had no institutional and legal recourse. There was no more treatment. Within four years, their advanced-stage patients would most likely die.

As clinicians expressed their concerns over patient care, they highlighted the contractual uncertainties that pervade the world's clinical trial scene and how an obligation to minimize harm can be undercut. Accounting for such uncertainties requires moving beyond 'doctor–patient' relations or 'investigator misconduct'. Their experience points to urgent problems of responsibility buried beneath the 'paper ethics' of the globalized trial, and the ethical variability that leaves ample room for contingent or opportunistic behaviors.

This case illuminates the unevenness of institutional powers in the now-global landscape of experimentation, as well as the lack of local coordination and negotiating ability. While the benefits deriving from the globalized clinical trial were clearly conceptualized by the various parties involved, one variable that was not well thought-out was the harm that could occur if the study treatment was withdrawn. Moreover, no one is helping patients to formalize their interests (other than the trial sponsor). A modeling of the value that patients actually bring to the trial (and ultimately, to the drug) would be illuminating too. Also, patients' informed consent should be supplemented with informed *contracts* on the part of local investigators.

The significance of clinical research for the welfare of large numbers of people is growing (Kahn *et al.,* 1998), but the benefits deriving from globalized research are unevenly distributed. Current institutional ideas about patient protection remain rather narrowly construed, and the harm dimension (how harms are produced in the broader contexts of experimentation) needs specification. Clinical trials are large-scale and multivariable systems. But, as this article shows, uncertainty pervades their inputs and outputs and—as the paradigm of expected failure suggests—threatens the integrity of the system itself. Biased protocol design can 'engineer up' the success of the trial, but approaches to detecting safety problems remain inadequate. The ability to choose treatment-naïve subjects creates efficient results, free of statistical noise, but even here my CRO informants expressed serious doubts about the generalizability of data—for example, how can results derived from treatment-naïve groups ever be generalized to populations in treatment-saturated markets?—as well as concerns about ineffective and unsafe drugs entering the market. This article also explored the technical practices by which companies can make harms go away, and the role of offshoring in this regard. These practices go hand in hand with the absence of governmental institutions capable of monitoring the entrance of ineffective drugs into the market and their long-term side effects, not to mention that, in many countries, patients still lack legal recourse for harms incurred during and after trial participation.

Industry and regulatory concerns about ethics seem to matter currently at the level of the data—more specifically, at the level of ensuring the 'integrity of data'. Why invest in a foreign site, if one is uncertain whether the data collected there will even be usable in the US

drug approval process? This, I believe, is currently driving the push for the establishment of more local ethical review boards in new sites. Was there informed consent? Did the local investigator agree to accept all responsibility in cases of harm? Did the local ethical review board review and ok the protocol? At stake is the making of an airtight documentary environment assuring the portability of foreign-derived data. Furthermore, when the focus of the experiment is on portability of data, the uncertainties of context and patient-related variables are engineered out. And this in itself is a risk that may show up later as a harm.

Whether they work directly for the clinical trial industry as scientists and study monitors, or are occasionally on its payroll as recruited investigators, my informants in the United States, Brazil and Poland show how harm detection can be deferred and patient protection compromised. Rather than positioning themselves as isolated entrepreneurs being 'squeezed down by costs' or as passive stewards of a clinical trial machine, they reaffirm the need for a sounder science and of stretching the capacities of clinical trials as health-care interventions—medical research and care go hand in hand. They champion a different sort of market-oriented pharmaceutical contract, one that goes beyond a proceduralized form of ethics and that can value patients again. As the turf war among pharmaceutical sponsors for human subjects rages on, I have drawn on their diverse perspectives to consider how accountability is brought to bear on the offshored clinical trial and the challenges it raises for global public health.

## References


Abramson, J. (2004). *Overdosed America: The broken promise of American medicine*. New York: HarperCollins.

Angell, M. (1988). Ethical imperialism? Ethics in international collaborative clinical research. *New England Journal of Medicine, 319*, 1081–1083.

Angell, M. (1997). The ethics of clinical research in the Third World. *New England Journal of Medicine, 337*, 847–849.

Angell, M. (2000). Investigators' responsibilities for human subjects in developing countries. *New England Journal of Medicine, 342*, 967–968.

Angell, M. (2005). *The truth about the drug companies: How they deceive us and what to do about it*. New York: Random House.

Angell, M. (2006). Your dangerous drugstore. *New York Review of Books, 53*(10). URL (accessed February 2007): http://www.nybooks.com/articles/19055

Avorn, J. (2004). *Powerful medicines: The benefits, risks, and costs of prescription drugs*. New York: Knopf.

Bayer, R. (1998). The debate over maternal-fetal HIV transmission prevention trials in Africa, Asia, and Caribbean: Racist exploitation or exploitation of racism? *American Journal of Public Health, 88*, 567–570.

Biehl, J. (2001). Technology and affect: HIV/AIDS testing in Brazil. *Culture, Medicine and Psychiatry, 25*, 87–129.

Biehl, J. (2006). Pharmaceutical governance. In A. Petryna, A. Lakoff, & A. Kleinman, (Eds), *Global pharmaceuticals: Ethics, markets, practices*. Durham, NC: Duke University Press.

Botbol-Baum, M. (2000). The shrinking of human rights: The controversial revision of the Helsinki Declaration. *HIV Medicine, 1*, 238–245.

Christakis, N. (1992). Ethics are local: Engaging cross-cultural variation in the ethics for clinical research. *Social Science and Medicine, 35*, 1079–1091.

Cohen, L. (1999). Where it hurts: Indian material for an ethics of organ transplantation. Special issue on 'Bioethics and beyond', *Daedalus, 128*, 135–165.

Crouch, R.A., & Arras, J.D. (1998). AZT trials and tribulations. *Hastings Center Report, 28*, 26–34.

Das, V. (1999). Public good, ethics, and everyday life: Beyond the boundaries of bioethics. Special issue on 'Bioethics and beyond', *Daedalus, 128*, 99–134.

Das, V., & Das, R.K. (2006). Pharmaceuticals in urban ecologies: The register of the local. In A. Petryna, A. Lakoff, & A. Kleinman, (Eds), *Global pharmaceuticals: Ethics, markets, practices*. Durham, NC: Duke University Press.

de Zulueta, P. (2001). Randomised placebo-controlled trials and HIV-infected pregnant women in developing countries: Ethical imperialism or unethical exploitation? *Bioethics, 15*, 289–311.

Dickersin, K., & Rennie, D. (2003). Registering clinical trials. *Journal of the American Medical Association, 290*: 516.

Epstein, S. (1996). *Impure science: AIDS, activism, and the politics of knowledge*. Berkeley: University of California Press.

Etkin, N. (1999). The rational basis of 'irrational' drug use: Pharmaceuticals in the context of development. In R.A. Hahn, (Ed.), *Anthropology in public health: Bridging differences in culture and society*, 165–182. New York: Oxford University Press.

Farmer, P. (1999). *Infections and inequalities: The modern plagues*. Berkeley: University of California Press.

Farmer, P. (2002). Can transnational research be ethical in the developing world? *The Lancet, 360*, 1301–1302.

FDA (Food and Drug Administration) (2004). *Innovation/stagnation: Challenge and opportunity on the critical path to new medical products*. March. Washington, DC: Dept of Health & Human Services.

Geertz, C. (2000) [1984]. Anti anti-relativism. In *Available light: Anthropological reflections on philosophical topics*, 42–67. Princeton, NJ: Princeton University Press.

Goozner, M. (2004). *The $800 million pill: The truth behind the cost of new drugs*. Berkeley: University of California Press.

Gorman, J. (2004). The altered human is already here. *New York Times*, 6 April: F1.

Guess, H.A., Kleinman, A., Kusek, J.W., & Engel, L.W. (Eds) (2002). *The science of the placebo: Toward an interdisciplinary research agenda*. London: BMJ Books.

Harkness, J.M. (1996). Nuremberg and the issue of wartime experiments on US prisoners: The Green Committee. *Journal of the American Medical Association, 276*, 1672–1675.

Healy, D. (2003). Lines of evidence on the risks of suicide with selective serotonin reuptake inhibitors. *Psychotherapy and Psychosomatics, 72*, 71–79.

Juni, P., Nartey, L., Reichenbach, S., Sterchi, R., Dieppe, P.A., & Egger, M. (2004). Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *The Lancet, 364*, 2021–2029.

Kahn, J.P., Mastroianni, A.C., & Sugarman, J. (1998). *Beyond consent: Seeking justice in research*. Oxford: Oxford University Press.

Kassirer, J.P. (2004). *On the take: How medicine's complicity with big business can endanger your health*. Oxford: Oxford University Press.

Kent, D., Mwamburi, M., Bennish, M., Kupelnick, B., & Ioannidis, J. (2004). Clinical trials in sub-Saharan Africa and established standards of care: A systematic review of HIV, tuberculosis, and malaria trials. *Journal of the American Medical Association, 292*, 237–242.

Kim, J.Y., Mukherjee, J.S., Rich, M.L., Mate, K., Bayona, J., & Becerra, M.C. (2003). From multidrug-resistant tuberculosis to DOTS expansion and beyond: Making the most of a paradigm shift. *Tuberculosis, 83*, 59–65.

Lasagna, L. Prisoner subjects and drug testing. *Fed Proc 1977* Sept 36(10):2349–2351.

Lemmens, T., & Freedman, B. (1997). Ethics review for sale? Conflict of interest and commercial research ethics review. *Milbank Quarterly, 78*, 547–584.

Lexchin, J., Bero, L.A., Djulbegovic, B., & Clark, O. (2003). Pharmaceutical industry sponsorship and research outcome and quality: Systematic review. *British Medical Journal, 326*, 1167–1170.

Lurie, P., & Wolfe, S.M. (1998). Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *New England Journal of Medicine, 337*, 853–855.

Lurie, P., & Wolfe, S.M. (2000). Letter to the National Bioethics Advisory Commission regarding their report on the challenges of conducting research in developing countries (HRG Publication #1545). URL (accessed January 2007): http://www.citizen.org/publications/release.cfm?ID=6746

Macklin, R. (1999). *Against relativism: Cultural diversity and the search for ethical universals in medicine*. Oxford: Oxford University Press.

Marks, H. (1997). *The progress of experiment: Science and therapeutic reform in the United States, 1900–1990*. Cambridge: Cambridge University Press.

Marks, H. (2000). Where do ethics come from? The role of disciplines and institutions. Paper presented at the Conference on 'Ethical Issues in Clinical Trials', University of Alabama at Birmingham, 25 February.

Marks, H. (2002). Commentary. 3rd Annual W.H.R. Rivers Workshop, 'Global Pharmaceuticals: Ethics, Markets, Practices', Harvard University, 19– 21 May.

Masters, B., & Kaufman, M. (2004) Painful withdrawal for makers of Vioxx. *Washington Post* 18 October, A01.

Moynihan, R., & Cassels, A. (2005). *Selling sickness: How the world's biggest pharmaceutical companies are turning us all into patients*. New York: Nation Books.

Office of the Inspector General, Department of Health and Human Services (2001). *The globalization of clinical trials: A growing challenge in protecting human subjects*. Boston, MA: Office of Evaluation and Inspections.

Petryna, A. (2002). *Life exposed: Biological citizens after Chernobyl*. Princeton, NJ: Princeton University Press.

Petryna, A. (2005). Ethical variability: Drug development and the globalization of clinical trials. *American Ethnologist, 32*, 183–197.

Petryna, A. (forthcoming) *The human subjects research enterprise*. Princeton, NJ: Princeton University Press.

Petryna, A., & Kleinman, A. (2006). The pharmaceutical nexus: An introduction. In A. Petryna, A. Lakoff, & A. Kleinman, (Eds), *Global pharmaceuticals: Ethics, markets, practices*. Durham, NC: Duke University Press.

Rothman, D. (2000). The shame of medical research. *New York Review of Books, 47*(19), 60–64.

Sim, I., & Detmer, D.E. (2005). Beyond trial registration: A global trial bank for clinical trial reporting. *PLoS Medicine, 2*, e365.

Temple, R. (2002). Placebo-controlled trials and active controlled trials: Ethics and inference. In H.A. Guess, A. Kleinman, J.W. Kusek, & L.W. Engel, (Eds), *The science of the placebo: Toward an interdisciplinary research agenda*, 209–226. London: BMJ Books.

Wardell, W., & Lasagna, L. (1975). *Regulation and drug development*. Washington, DC: American Enterprise Institute for Public Policy Research.