

## INTRODUCTION



# EXPERIMENTAL FIELDS

### The Search for Human Subjects

If I drive two miles down the road that takes me to the supermarkets and retail shops of the midwestern town where I grew up, I will pass the local branch of Across-the-Globe-Research (AGR). A freestanding office space, newly built, with a redbrick exterior and white casement windows, the building is surrounded by a parking lot. The AGR facility looks like a standard suburban medical practice, but it is not quite that. It is an investigative research site that conducts clinical trials for the pharmaceutical industry. Clinical trials are studies designed to systematically evaluate new drugs or new ways of using known treatments in humans. They are a way to meet the requirement that the safety and effectiveness of drugs or treatments be established before they enter the market. Yet trials are imperfect and, at times, biased instruments that may or may not yield the most complete evidence about a drug's benefits and risks.

Inside AGR, one spring day in 2005, a bedraggled patient-volunteer, accompanied by an escort who appeared to be his caregiver, sat waiting for his name to be called by a physician who was standing behind a glass pane—much like a bank teller, I thought. The physician asked the patient whether he had experienced any side effects from taking an experimental drug. The answer was no, and the doctor passed him a new dose. The patient left. He would return regularly over a prescribed period. According to the research protocol, some visits were brief, like this one. Others involved more detailed

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physical observations to gather data related to the clinical trial's specific objectives.<sup>1</sup>

AGR's physician-employees are specialists in neurology, gastroenterology, endocrinology, and psychiatry. They enroll volunteers from a pool of new patients in their private practices and from AGR's own, and larger, patient database. Regardless of the source of the trial participants, though, AGR, as the investigative site, bears ultimate responsibility for compliance with regulations governing human subjects research.

The window separating the doctor from the patient-volunteer was a cold reminder of a loss of intimacy in medical care—a loss that social scientists have lamented as moral codes guiding physician behavior are increasingly defined by nonmedical outsiders, lawyers, for example.<sup>2</sup> Physicians at this facility preferred to be distant. According to AGR's business manager, whom I will call Evan (and whom I spoke to that afternoon), most physicians here feel that research practice interferes with their regular clinical practice. They would rather not mix them. The benefits of this arrangement apparently outweighed the conflicts of interest that might have been built into it: "When experimental drugs are available, of course, physicians feel compelled to enroll their patients." The transactions at this site and Evan's confident statements speak to the distinctive public presence of clinical trials and to the shifting boundaries between medical research and medical care.

Global pharmaceutical sales reached \$712 billion in 2007.<sup>3</sup> North America accounts for almost half of total sales, and there is an accelerated growth in the new markets of Latin America, Asia, and Eastern Europe.<sup>4</sup> Today, more than 70 percent of all medical visits in the United States result in at least one "drug mention," a term used to denote the prescription, continuation, or provision of a drug. On average, two drug mentions are recorded per medical visit.<sup>5</sup> Antidepressants are the most highly prescribed drugs, followed by medications to combat high blood pressure, anticholesterol agents, antiarthritics, and antiasthmatics. This phenomenal pharmaceutical expansion has been coupled with an unprecedented surge in the number of health professionals and patients recruited into clinical research in the United States and in middle- and low-income countries. In recent decades, access to experimental therapies has broadened, particularly in the areas of AIDS, cancer, and genetic treatments, and ambitious federal and industry efforts are under way to recruit more people for clinical trials in the United States and abroad.

Different kinds of patients have different stakes in clinical trials. As trial participation becomes a form of mainstream medicine, the desperately ill

might accept clinical trials as their best medical option rather than as “mere” experimentation. For many, taking part in a trial means getting access to better medical monitoring than what is routinely provided in industrialized medicine. For those with no health insurance, trials are sometimes the only pathway to needed treatment. And for people who do not have stable jobs, drug trials and other kinds of trials might be a source of income.<sup>6</sup>

Precise figures of the number of trial participants and clinical trials carried out in the United States, let alone worldwide, are hard to come by. This is in part because the Food and Drug Administration (FDA), the principal agency regulating drugs, medical devices, and biological products used by Americans, is unable to identify all ongoing clinical trials and their associated trial sites (OIG 2007). As of 2008, 65,755 trials sponsored by federal agencies and private industry were listed on ClinicalTrials.gov, a service of the U.S. National Institutes of Health designed to provide up-to-date information for those interested in locating clinical trials. It is estimated that each year, more than 2.3 million people participate in clinical trials in the United States alone. Between 2000 and 2005, the FDA audited fewer than 1 percent of the 350,000 trials sites that the Office of Inspector General has estimated are active worldwide (*ibid.*:19).

The truth is that governmental agencies have little control over this experimental field, and as a general public we know little about the design of research protocols, the conditions under which trials are carried out, or the dependability of the evidence about a drug’s benefits and risks. As recent withdrawals of drugs from the market illustrate, experimentation extends beyond the duration of the clinical trial—with potentially deleterious effects. For example, approximately 6 million American women were using hormone replacement therapy when, in 2002, the Women’s Health Initiative discovered that the potential harms, including increased risks of breast cancer, heart disease, stroke, and blood clots, outweighed the benefits of the treatment. Similarly, physicians had prescribed a popular nonsteroidal anti-inflammatory drug to 84 million people before the drug was removed from the market in 2004, after evidence of cardiovascular risk came to light.

Today, the majority of clinical research endeavors are industry sponsored. In 1980, industry funded 32 percent of clinical research. By 2000, the figure had soared to 62 percent. AGR began business in the mid-1990s and has been expanding ever since. It has a dozen affiliated research sites, located in diverse socioeconomic enclaves and towns in the United States and in Eastern Europe and Eurasia that run all phases of clinical trials. One midwestern U.S. site is operated by a Polish-born psychiatrist with a busy adult prac-

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tice. This doctor works in three area hospitals and supervises trials involving a largely Eastern European immigrant population. The site advertises its staff as being multilingual. Another site is located in a psychiatric counseling center in the heart of a once-prosperous coal-mining town. This facility is also run by a psychiatrist who has a private practice and is employed by local hospitals. Another of AGR's sites is located at the southeastern shore, near large retirement communities. After Hurricane Katrina, the Gulf Coast site stopped enrolling research subjects.

Evan, my AGR contact, is an articulate and hardworking fifty-year-old businessman. When we met that day at his office, he looked fit and was casually dressed in a worn, light-blue oxford shirt with the sleeves rolled up. Evan also facilitated overseas drug testing, and he explained the draw of carrying out drug studies in Eastern Europe and Eurasia. Subjects there are apt to be accommodating, he said. They receive Western medical treatments they otherwise could not pay for, and they adhere to trial procedures and do what is asked of them. Physicians in those regions are known to be competent, but poorly paid; they gravitate toward the money research brings. According to Evan, they are willing to become study monitors, providing support for other physician-investigators and making sure that research protocols are properly executed. That task pays considerably more than what a Russian physician earns for treating patients, Evan told me.

This expert seemed to move effortlessly between the business of clinical trials overseas and that in the United States. Fifty miles west of AGR, in a nearby state, are the headquarters of several contract research organizations (CROs), including two former employers of Evan. Unlike AGR, a small company that focuses solely on running trials, CROs offer a wider set of services to pharmaceutical, biotechnology, and medical-device companies. They organize and monitor all stages of global multisited trials and guide clients through complex national regulatory environments. In his previous capacity as a leader of business development for a CRO, Evan told me, he had gained "a good sense of how the international marketplace for clinical testing works." He said he had also acquired regulatory and legal knowledge there and developed networks of contacts in the United States and abroad that came in handy when he created his own company. In 2003, AGR investors approached him. As he recalls, "They said, 'We want you to work this company from a business development perspective, and we'll give you a piece of it all.'" His statement suggests that in clinical research, the chain of entrepreneurial stakeholders is getting longer and more decentralized, rather than becoming streamlined.

Monitoring rooms, laboratory space, and storage make up this local AGR office. Researchers can conduct more specialized trial-related assessments and tests within a mile of the office, at private medical facilities. AGR investigators are also attending physicians in the acute care and outpatient services of nearby hospitals, and AGR collaborates with other physicians in the region, who refer patients to this investigative site. According to Evan, AGR is overwhelmed with industry contracts. Pharmaceutical sponsors need study subjects, and, as he put it, “We can’t take in patients fast enough.” Demand overtakes supply, in part, because the U.S. landscape of commercial clinical research “suffers from dire shortages of investigator sites and patients,” in Evan’s words. Starting in the early nineties, clinical research in the United States began moving out of academic medical settings, where it had been principally conducted, to local hospitals and primary-care settings and private investigative sites such as AGR. Evan is part of a growing group of subcontracted professionals who make up the so-called clinical trials industry that facilitates a decisive step in the global science of drug development. He marshals qualified investigators and patients, and his company piggybacks drug testing onto existing health care infrastructures. His work is part of a thriving and expanding global experimental enterprise, one whose scope and broader implications are largely unknown.

### **Anthropology and the Global Clinical Trial**

The pharmaceutical industry is the major producer of today’s therapeutic armamentarium, and it is increasingly outsourcing and offshoring clinical research. This book is about the business of clinical trials.<sup>7</sup> It examines the organizational cultures of industry-sponsored clinical research, probing scientific, ethical, and regulatory practices. The book traces the worldwide expansion of this experimental enterprise, and it explores how it is integrated into medicine and public health in both rich and poor settings. I began investigating clinical research (mainly related to chronic diseases and to new genetic therapies) in 2001 and continued, charting its movement to Eastern Europe and Latin America, for the next several years. The entrepreneurial world of clinical trials is composed of contract research organizations; patient recruitment firms; for-profit research ethics review boards; and stand-alone investigative research sites that are nestled in urban and suburban communities in the United States and around the world. The clinical trials industry accounts for roughly one-third of all clinical development expenditures. While the pharmaceutical industry’s revenue growth

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has leveled off somewhat, the clinical trials industry has boomed. What, precisely, is the relation between the drug industry's stagnation and the clinical trials industry's rise?<sup>8</sup>

I initially focused my study on how the clinical trials industry evolved and has been operating in the United States. I paid particular attention to the work of contract research organizations, the biggest and most profitable sector of this industry. Speaking with corporate executives, administrators, and scientists, I asked them how they defined their work and overcame operational and technical problems, and how they navigated ethical guidelines, national regulations, and business practices. Because one of my chief concerns was the question of scientific integrity, I then charted the evidence-making practices that have evolved with the offshoring of clinical trials (to Poland, for example). I engaged trial managers and monitors, along with publicly funded academic scientists and national health authorities, and I also considered the effects of privately funded clinical research in ailing public health systems (in Brazil, for example).

In my inquiry, I saw the promises and perils of the global clinical trial taking form, and in this book I distill the fundamentals of what I learned from the many parties involved. A few caveats are in order. I am not a bioscientist, and my purpose here is not to evaluate the pharmacological or clinical science entailed in drug development. As an anthropologist, I have written about the social and political implications of science and technology in the context of nuclear disaster and global pharmaceuticals.<sup>9</sup> Much has been written about the social construction of the evidentiary process in clinical trials—how the evidence-making process is itself laden with financial conflicts of interest.<sup>10</sup> Not much has been said about the practical and technical concerns that surround current strategies of clinical research and how they affect collective and public health processes downstream. My study focuses on these latter issues, and I am committed to bringing anthropological knowledge to bear on ethics and policy debates. But it is ultimately the work of scientists, doctors, and regulators to appraise the safety and efficacy of new therapies. This book is not “antiscience,” nor is it intended to undercut the social value of the research enterprise. Pharmaceutical innovation contributes critically to the alleviation of the global burden of disease. As I address the changing precepts governing clinical trials and how experimental groups are identified and constituted, I ask: what value systems bring researchers, physicians, and patients into trials? More broadly, if clinical research increasingly serves as a surrogate to underfunded state health-care systems, how do we assess drug value, minimize investments in

drugs that are either unsafe or marginally beneficial, and maximize institutional investments in global access to the drugs that are both safe and beneficial? Throughout the book, I give voice to the perspectives of national regulators, industry figures, and their critics. How do they see the dimensionality of the problem and the implications of their work in terms of control over methods, researchers, subjects, and ethical issues? In shedding light on actual practices and decision-making processes, my goal is to foster less partisan and more comprehensive understandings of the human dimensions of scientific innovation. I believe that it is the task of social science to produce nuanced and people-centered forms of knowledge, correcting asymmetries of information and helping to promote, to the best of our ability, informed consent, human protection, and safety in medical and research settings.

In chapter 1, I present some of the book's main actors and juxtapose their knowledge bases and practices. I highlight the main factors underlying the growth of the clinical trials industry and offshoring of clinical trials. What is taking place is experimentality and not just fine-tuned, randomized controlled trials that people are free to choose whether or not to enter into. I discuss controversies that have recently framed debates over globalizing clinical research and interpret them from a strategic industry standpoint. While trials of AZT treatment using placebos in Africa and elsewhere may be limit cases, such trials permit us to explore the gaps between international ethical guidelines and the social and political realities of research. In zones of crisis, protection and safety considerations are weighed against immediate health benefits or the knowledge to be gained, leading to a cost-effective variability in ethical standards. As health risk becomes a resource for capital, ethical variability becomes a core value and a presumed modus operandi in globalized clinical research. What work is to be done to guarantee accountability and to link experimental biologies to regimes of protection?

The clinical trials industry is a crucial, highly mobile and profitable arm of the pharmaceutical industry; it is both domestic and international in scope. Chapter 2 explores the outsourcing and offshoring of clinical trials, past and present, and how they interconnect with the dynamics of drug development and regulation in the United States. Experimentality as an instrumental use of humans in research was, arguably, already present at the outset of modern drug regulation (Marks 1997). I show how a risk-benefit approach to different research contexts evolved and is being applied in global settings. I also elaborate on the problems and limits of this instru-

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mental use of humans, as well as tease out the logic, loopholes, and gaps in existing regulatory structures that legitimate it internationally. The scientists I knew were troubled about safety problems being detected only after the fact. They articulate surprising connections between this failure to detect and trial offshoring.

Uncertainties have plagued the research enterprise at home, but what happens when experiments travel? In chapter 3, I take the reader to Eastern Europe, where I investigated the organization and spatial mobility of offshored trials and probed the limits of oversight and accountability (understood as the ability to track clinical trials, maintain scientific integrity, or reduce research-related risk). What are the institutional arrangements allowing experimentality to rise and (sooner or later) fall? Why is it that public debates over commodified patients and expertise seldom arise? How to reconcile images of free movement and riskless profit with the actual forms of risk and liability on the ground? The quotidian operations generating efficacy and safety data become ethnographic contexts from which one can observe the benefits and risks of private-sector science as it is rapidly integrated into public health systems and emerging drug markets.

Once clinical trials data have been sent off to corporate headquarters, new medical fields emerge locally. In chapter 4, I turn to Brazil and investigate the aftermath of clinical trials. It is in this posttrial stage that issues such as continuity of treatment and ongoing control of data by sponsors—sometimes not anticipated in contracts or informed consent forms—must be addressed. Posttrial subjects-turned-patients and -consumers continue to need medicines that are now on the market yet out of their financial reach. Meanwhile, trial sponsors continue to exert control over study data in the drug-marketing phase. Throughout the chapter, I show how academic scientists are dealing with the overwhelming demand made by patients and marketers on doctors to prescribe, and on the state to provide, new high-cost medicines whose benefits are not unequivocally established. As they dissect the comparative value of new drugs, these Brazilian scientists convey a systemic knowledge of the political economy of pharmaceuticals and the inequities that it can generate locally. They are creating alternative treatment protocols in dialogue with international experts and in partnership with national health policy makers. Their story is not about an evidence-based scientific orthodoxy. It is about how local actors, states, and patients in a low-income setting create institutions to address at times appalling disparities between drug value and price and the complex political and market factors that impede their efforts.

It is also about new collaborations and experiments that aim to make needed medicines accessible and their provision sustainable.

Whether they work directly for the clinical trials industry as scientists and monitors, are occasionally recruited as paid investigators, or remain outsider-critics, my interlocutors in the United States, Brazil, and Poland cite challenges and risks that, despite the oversight of regulatory and ethics review boards, are being produced in the global economy of research. In their efforts to improve scientific integrity, reduce risk, or negotiate drug costs, they illuminate situations that are not unique to their respective countries. In the concluding chapter, I draw these various threads and experiences together—scientific, commercial, public—in a discussion of medical innovation in global public health.

Clinical trials are part of charged social and political landscapes that link diverse participants—researchers, trial subjects, health professionals, corporate executives, regulators, policy makers, patient-consumers, and shareholders—to a host of calculable and incalculable hopes, benefits, profits, and risks. Experimentality, now an explicitly global phenomenon, enfolds public and private actors and interests into interconnected data-producing sites. It also provokes questions about how exactly the boundaries between research and practice are negotiated in various health settings. *When Experiments Travel* identifies elements of this multifaceted enterprise and weaves them into a global ethnography. Seen from this perspective, ideas of the therapeutic are more than scientifically or statistically determined constructs. They are also concepts of value, deeply embedded in economic, political, and technological imperatives. This book brings into view some of the convoluted contexts of the production of clinical trial data. In so doing, it excavates sources of knowledge that can help us rethink the criteria with which we define medical progress and, in the process, redirect our political commitments and investments.