GLOBAL HEALTH MARKETS: RECLAIMING THE EVIDENCE BASE

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(this is a draft)

Offshoring Clinical Trials

Since the mid 1990s, the pharmaceutical industry has disaggregated core processes of drug development (such as clinical research), rebuilt them in new locations, and obtained access to pools of low-cost resources as well as valuable and skilled laborers—while still clinging to a traditional operational model that is focused on “blockbuster” drug development. Pharmaceutical sponsors are engaged in a turf war for human subjects worldwide to support this model of development, and a “clinical trials industry” is expanding its global footprint to deliver large patient pools. Since 2003, I have carried out field research on offshored clinical research environments and their ethical and regulatory frameworks. I take the operations of contract research organizations (CROs), which emerged in the early 1990s and constitute a specialized industry focusing on subject recruitment and clinical development for the drug industry, as a window into these new experimental terrains. CROs claim to recruit patients quickly
and more cheaply than academic medical centers. Most are involved in locating research sites, recruiting patients, and, in some cases, drawing up study designs and performing analyses. Sometimes they work with primary health care facilities, hospitals, or consortia of therapeutic specialists. They provide close to half of the number of clinical research personnel engaged in drug development activities.²

The offshored infrastructures that CROs help to tailor on behalf of pharmaceutical firms are adaptable, mobile, and, to some extent, parasitic. They insert themselves in ongoing and unresolved conflicts over market reforms and over the role of public institutions in local societies. At any given moment, they can be moved somewhere else.³ National health and regulatory experts play a key role in shaping local understandings of clinical trials, their benefits, and their risks, and they have high stakes in attracting clinical trials to their countries and in keeping them there.

I carried out a comparative ethnographic inquiry in two of the fastest-growing markets for clinical trials (Latin America and Eastern Europe). As I chronicled the offshored trials in Polish and Brazilian sites, I marveled at how “well” this outsourced enterprise could seal out the needs and demands of local health systems. It was all about getting the data, ensuring its “integrity,” and making data from international sites portable and usable within the U.S. drug approval process while avoiding, at all costs, the convoluted contexts of data capture. In the memorable words of Dr. Renata Mazur, who heads the Polish affiliate of a global CRO, “I don’t see patients, I see data.”⁴

Sitting in an elegant Warsaw office in June 2005, Dr. Jan Novak, the medical director of Astra Zeneca-Poland (a client of Dr. Mazur’s company), described the value
of patient data in industrial terms: “Central-eastern Europe is the second largest producer of clinical data after the United States.” Each world region’s productivity, Dr. Novak said, is weighed in terms of its output of “clinical research units” (CRUs), a standard this company created to measure the labor intensiveness of monitoring each trial subject. “In our formula we multiply the value of the patient by his or her complexity. So one patient in an oncology study is like two patients in a respiratory or simple hypertension study. We are doing a lot of CRUs in Poland.” Novak was proud that his company was “meeting recruitment targets” and added, “We are still trailing behind the U.S. in terms of CRUs, but we are ahead of Latin America by five years.”

Similar stories of regional competitiveness, productivity, and clinical trial success repeat around the globe. In an interview in April 2004, Dr. Sergio Slawka, a senior research scientist for a large pharmaceutical firm in São Paulo and the treasurer of Brazil’s main pharmaceutical trade group, boasted that Brazil’s clinical trial market is “one of the fastest growing in the world.” He estimated that about 95 percent of his company’s work involved multicentered trials in second and third phases. “For instance, at this moment I have around 20–25 different protocols. These protocols can involve research subjects from up to 70 countries, of which Brazil is one. I am working with only one locally designed protocol.” He emphasized the benefit of this (potentially lop-sided) approach: “Yes, a lot of data is transferred out of the country, yet a lot of clinical investment comes back in.”

This Brazilian entrepreneur and others in similar positions in Poland were confident that the quality of their data was guaranteed because international ethics guidelines are “converted locally.” They defended the value structure of transnational
pharmaceutical production—ensured by patent-related agreements, ethical guidelines, and other directives governing trial conduct. They affirmed the efficacy and transparency of the global trial enterprise and their ability to play by its rules. Indeed, the same system that ensures that their subcontracted investigators in diverse locales will adhere to ethical guidelines—“No one pays better attention to the ethical guidelines than us,” the Brazilian industry scientist told me—also works to protect patient data in terms of its commercial value and as intellectual property.

Yet some physicians, occasionally those on the trial industry’s payroll in these two countries, question the value that clinical trials bring to public health. As one Brazilian physician said, “I care for the patient. I give him the meds and measure the endpoints. Just measure and send the data off. By the end of the trial you have sent a lot of raw data to the company.” As industry-sponsored research merges seamlessly with the normal habits and routines of public health care, “All there is left for me to do is to follow the rules and recommendations. … They have bought everyone.”

In Poland, some physicians who were considered to be too sympathetic toward their patients could not be trusted to carry out industry-sponsored research. Dr. Mazur, for example, was constantly on the lookout for competent physician-investigators she could recruit. I told her that one physician had told me that 300 of his rheumatoid arthritis patients are unresponsive to the standard of care treatment but that he has only 30 slots for his clinical trial testing a new biologic. She listened carefully and said that she avoided these (public health–minded) types. She referred to them as potential “protocol violators” who had a tendency to overenroll patients for medical care purposes. They were simply too entwined in social relations and were unable to “self-manage.”
In the trial industry, physicians’ compassion for patients had to be tamed and their attention reoriented toward the ultimate goal of “data integrity.” Was there informed consent? Did the local investigator agree to accept all responsibility in cases of harm? Did the local ethical review board evaluate and OK the protocol? But there is a political economy of research that these questions obscure and that can undermine the physician-investigator’s own ability to do no harm. Consider Dr. Maria Hiller, a talented Brazilian medical geneticist who conducts clinical trials on genetic therapies that can cost up to $200,000 per patient annually. She expressed concern about what happens at the end of clinical trials, when patients who need treatments will not be able to afford them. “In meetings with trial sponsors in São Paulo, I talked about costs. And you know what? They say it is unethical to talk about costs because, they say, you have to think about the patient first. I have not been invited to any more company meetings.”

In other words, rote conformity and intellectual passivity on the part of local investigators underpin the value structure that Slawka, Novak, and Mazur so heavily prize. That is, investigators are “valued” to the extent that they can break their alliances with patients and distance themselves from public health concerns. But when the sole focus of clinical research becomes measuring and sending the data off, the uncertainties of the context in which that data was derived and the patient-related variables are engineered out (Petryna 2007).

It is widely recognized that, from a health management perspective, clinical research and public health practice remain by and large disconnected (Abbasi 2005). For example, what is owed to patients, particularly after the trial? And when the new drugs are thrown back into emerging drug markets like Brazil and Poland, the disconnection
can get even worse: “We have no idea what their value is for our patients. All we know is that many of the new drugs can’t kill, but we don’t know if they can save.”

In this essay, I show how a team of academic scientists at Hospital de Clinicas in Porto Alegre, Brazil, is reversing the troubling forms of business control that have evolved over research and medical care on the ground. Members of the team, led by Dr. Paulo Picon, were critical of the ways pharmaceutical firms and their outsourced subcontractors were influencing the course of medical research and public health in Brazil. They were analyzing the efficacy and dosage requirements of new drugs entering the Brazilian market, now the second largest in Latin America. They were particularly concerned with drugs that do not promise to cure or extend life but that “simply lower some nonclinical indicator.” Drug value is a much-contested issue. But what happens in this socioeconomic context is that some of the new drugs that come on the market are 20 times more expensive that the standard and massively redirect state financing of health care to only a few.

What is the role of academic science and the public sector in narrowing the gap between clinical research and public health? What types of alliances (between patients and physicians, for example) are required? The team at Hospital de Clinicas, as I show, is taking up a basic challenge in global health in developing countries that are also emerging drug markets: of determining how best to deliver affordable and effective interventions (without resorting to triage). “It is not a matter of rejecting new technology,” Dr. Picon told me. “If it does some good we have to use it. And we are using it as much as we can. We have to find clear and safe criteria for patient inclusion and exclusion and monitor patients over the long run.” Against many institutional odds,
Dr. Picon and his team have spearheaded a statewide system of clinical research, implementing experimental protocols, creating their own database on drug efficacy and harm (a form of postmarketing surveillance), and, in some cases, showing that lower doses of certain high-cost drugs are as efficacious as high doses and cost less. Some of their research practices, as I note below, cut into the heart of the industry’s control and business strategies, particularly with respect to high-cost “orphan drugs” (of which Brazil is now a major market).\(^{12}\)

As these investigators attempt to narrow the gap between clinical research and public health, they revitalize academic medicine and create new domestic research capacities. What are the ethics and politics of their experimentality? How is this domestic technological capacity part of a new architecture of global health?

**“Pharmaceuticals are the New Gold”**

“The entire society is being recruited by the pharmaceutical industry,” Dr. Picon told me in an interview in August 2004 in his office at the Hospital de Clinicas, a public university–based general hospital in the southern city of Porto Alegre. Opened in 1971, Clinicas is a national center of excellence in health care, teaching, and research and is considered one of the ten best public hospitals in Brazil. It has over 60 medical specialties, and more than 300 professors from the Federal University of Rio Grande do Sul (UFRGS) work there and train an average of 300 medical residents.

A cardiologist and a clinical pharmacologist, Dr. Picon trained at UFRGS and at Harvard Medical School. In the 1980s, he instituted a respected program in clinical
pharmacology. He has trained scores of medical students in evidence-based medicine and clinical pharmacology, and he has earned many distinctions for his work. Dr. Picon is also a consultant to the country’s Ministry of Health and its drug regulatory-affairs body (ANVISA) as well as a health authority in the state of Rio Grande do Sul. The 48-year-old scientist had just been named director of the hospital’s Clinical Research Unit. The unit, created in 2003, is one eight national centers that engage in bioequivalence studies in which generics are tested against standard or older drugs.13

Dr. Picon was also spearheading efforts to regulate the use of high-cost “exceptional” medicines, which are normally not included on the list of medications covered by the universal health care system, or SUS (Sistema Único de Saúde). Exceptional medicines are placing severe financial burdens on limited public health funds, and, according to Dr. Picon, “many of these medicines have an incomplete evidence base.” They constitute a formidable market in Brazil. In 2005, the country paid approximately $1.4 billion for them.14 From a public health–sector standpoint, this new market in high-cost medicines diverts resources from primary health care and reduces access to essential medicines—a basic human right.

In 2001, then health minister José Serra invited Picon and his team of consultants, medical residents, and doctoral students to lead a health technology assessment, which ultimately led to the publication of the Clinical Protocols and Therapeutic Guidelines for Exceptional Medications (which I discuss below). Serra asked Picon’s group to establish criteria for the use of exceptional medicines inside SUS or, in Picon’s words, “to make sense of all of this. … Up until then, the health ministry was a good payer. It just paid. It never measured health outcomes and value and never published anything. There were no
scientific criteria in place to integrate high-cost drugs in the universal health system. It was all a matter of how much pressure company reps put on the health ministry and what the package insert said in terms of the drug’s use.” Serra had played a critical role in sustaining Brazil’s AIDS treatment rollout. By reverse engineering antiretroviral (ARV) drugs and promoting the production of generics in public and private laboratories, the health ministry had been able to create mechanisms for drug price differentiation. This kept the rollout in place, which in turn led to significant drops in hospitalization rates and AIDS mortality (Biehl 2006, 2007).

For all the good it had done, the AIDS policy had also opened the floodgates for high-cost drugs. Access to all kinds of medicines, whether on the country’s essential drug list, part of special programs, or even in experimental stages and not yet marketed, had come to stand in for the right to health care. Just as the country had invented a successful drug price-negotiation strategy, now it needed mechanisms to reverse the variety of interests that had led to the influx of high-cost medicines. Minister Serra, for example, waged a fierce battle with the pharmaceutical firm Novartis over the company’s alleged abusive pricing practices. He alleged that, to promote its drugs, the company was exploiting Brazil’s constitutional right to universal health care and its court system. In this instance, it was mobilizing patient groups to demand the twice-as-expensive Novartis brand drug over the available generic cyclosporine (used to prevent organ rejection in kidney, liver, and heart transplant patients). It was also aggressively marketing its new drug Gleevec (used to treat chronic myeloid leukemia). Some of the Gleevec trials took place in Brazil. According to Picon, “Novartis told the Brazilian patients that the treatment would be discontinued after the trial ended, and that they needed to exercise
their right to health and pressure the government to purchase the drug. After Novartis got ANVISA’s approval on the basis of research on those desperately sick patients, they turned around and said, ‘What happens to patients after the trial is not our responsibility, it’s the government’s.’”

Dr. Picon is plainspoken and unapologetic in his criticism of the industry’s overall influence in his hospital, province, and country. “In Brazil, pharmaceuticals are the new gold… . Companies give handouts to physicians, sponsor trips, finance conferences. The physician prescribes the medication that the company wants him to prescribe and the patient never questions the physician,” he said. “Patients from all social classes are demanding treatments from municipal and provincial health secretaries. They can contact the officers from the Public Ministry, the state organ that defends citizens’ rights, and, in the end, local judges always decide in favor of the patient.”

The first judicial claims were made by AIDS and cancer patients in the early 1990s, and now this “judicialization” of health has become routine. Desperate patients demand high-cost treatments. They are modeling their efforts after successful movements by AIDS patients in Brazil and the United States to gain access to ARV drugs. And this mix of patient activism, human rights discourse, and market-driven medicine is leading to what João Biehl (2006) calls the “pharmaceuticalization of public health,” raising vital questions about public health priorities, financing, and equity in emerging drug markets.

Dr. Guilherme Sander, a gastroenterologist and one of Picon’s collaborators, described how lawyers stand outside public hospitals, offering their services to patients to litigate their rights to health. The patient’s legal claim to a treatment is always framed in terms of life or death, Picon’s colleague Dr. Costa added: “No judge wants to be
responsible for a patient’s death.” Moreover, in a context of scarcity, this judicial health-seeking strategy has become a kind of welfare technology, with citizens demanding “everything from special milk to geriatric diapers.”

The number of judicial actions for therapies has skyrocketed throughout Brazil. In 2002, the Prosecutor’s Office registered 1,126 lawsuits against the relatively well-off state of Rio Grande do Sul. That number had quadrupled by 2005. In 2001, the municipal health secretary of Goiânia, the capital of the central-western state of Goias, spent, on average, $10,000 per month to satisfy legal claims for the provision of medicines. In 2006, this expense was close to $50,000. He reported that this value corresponds to half the resources allocated for the purchase of basic medicines.

Dr. Picon and his team are concerned with scientific integrity and equity as the relentless “wheel” of the pharmaceuticalization and judicialization of health rolls on. “Forget about the rules. Forget about treatment protocols. Forget about the rational use of medicines.” If a doctor prescribes a treatment, Dr. Picon added, “then local health authorities must provide the treatment in three days. Physicians or local health administrators who do not provide the treatment can be arrested. Judges can issue injunctions to divert social security funds to satisfy these claims. We all wonder about what will happen with basic and preventive health care.”

Turning Evidence into Practice: Protocolos clínicos

When Dr. Picon and his team set out to create new treatment guidelines for high-cost drugs (Protocolos clínicos e diretrizes terapêuticas—medicamentos excepcionais,
hereafter “protocols”), they were not just rehearsing a cost-effectiveness mantra. They sought to address an uncontrolled field experiment introduced by a mix of pharmaceutical marketing and the state’s own judicialization of health. Their evidence-based efforts were patient centered. “Brazilian real-life patients are much sicker than the ideal patients in clinical trials,” Dr. Andry Costa, a cardiologist and one of Picon’s long-time collaborators, told me. “The unrealistic scenarios of randomized controlled trials are prone to produce biased data.” By considering the “real patient,” questions of appropriate dosage or whether treatments and retreatments are actually suitable or dangerous can be investigated and resolved.

To create the protocols, the team studied industry recommendations in drug package inserts and combed through scientific literature, comparing the efficacy of new drugs against older ones. They analyzed the design of clinical trials, looking for flaws in the data produced or at the trials’ understudied aspects, and they scrutinized the “gaming” of trial results. They parsed out differences in the contexts of trials and showed how results (health outcomes, rates of complication, mortality rates) in one context do not necessarily hold true for another. They then drafted guidelines reflecting the best evidence base.

Once a draft of a treatment guideline was completed, it was posted on ANVISA’s website for open commentary. “We were looking for some medical consensus,” Picon explained. But that is not what his team got. The treatment guideline for rheumatoid arthritis, for example, presciently warned against the use of cox-2 inhibitors (nonsteroidal anti-inflammatory drugs such as Vioxx) because of “indications of heart attack” (Protocols:81). During the guideline’s open commentary period, Picon’s group received
“26.8 kilograms of letters of complaint. … Lots of experts, doctors, and chairs of medical departments were telling us to abandon our effort.”

The treatment guideline for Gaucher disease was also especially contested. It provides a good example of “the difficulty of translating evidence into practice.”

Gaucher is an inherited metabolic disorder in which an enzyme deficiency results in progressive blood, bone, and, in some cases, nervous impairment. It is treated with imiglucerase, an enzyme replacement therapy in which a genetically engineered form of the missing enzyme is administered exogenously. The first version of the drug was brought to market in 1991 under the U.S. Orphan Drug Act. The drug has significantly improved the lives of Gaucher patients, but the question is, at what dose? The drug was approved by the U.S. Food and Drug Administration on the basis of a Phase 2 study, and the standard high dose (60 units per kilogram of body weight) used worldwide is based on that initial small study.

By 1995, Genzyme was marketing the drug in Brazil. Dr. Maria Hiller, a former contratado (subcontracted researcher) for Genzyme, said that, over the years, its manufacturer has kept tight control over clinical data. According to a recent annual report, the company is “continuing technological innovation to develop and maintain its hold on the product’s patent term.” Data has to be continually generated to fill out the drug’s safety and efficacy profile as a condition for maintaining the drug’s orphan status and, thus, its special exemption from price competition. But this business strategy can only work if researchers (and patients) are willing to provide data. The company, as Dr. Hiller told me, “must have global control over all the data, not just a portion. … It cannot afford to have any doubt over its evidence base,” in part, because doubt can erode public
confidence in the value of the drug. The company is quick to use its control over information to discredit researchers who prescribe at a lower dose, for example.

The price of imiglucerase has never dropped. Treatment can cost as much as $200,000 annually per patient. Imiglucerase generates more than $600 million in annual revenue. More than 4,500 patients globally are taking it (this number is based on the manufacturer-owned Gaucher patient registry), including 470 patients in Brazil. At the industry-prescribed dose, Brazil constitutes a $60 million annual market. By 2002, Dr. Hiller told me, colleagues in the Medical Genetics Services of Hospital de Clinicas said that Genzyme “owned” their Gaucher patients.

The Picon team’s Protocols Initiative attempted to recapture the patient and his or her treatment from business interests and to create an alternative national (rather than global) medical knowledge network. To construct the Gaucher treatment guideline, Picon consulted with Dr. Ernest Beutler of Scripps Institute, who had published the first major study of the natural history of Gaucher in 1991. Picon told me that no Brazilian doctor wanted to step in as a consultant for the Gaucher guideline. In 1994 Beutler published an editorial in the *American Journal of Medicine* on “economic malpractice in the treatment of Gaucher’s disease.” In it he recounted how Genzyme had tried to shift his patients to other doctors because of his low-dose prescription patterns. The company, he wrote, “advocat[es] doses of their drug that are four to eight times larger than those needed to provide an optimal response” (1994:2). Picon also contacted Dr. Ari Zimran, a former research fellow under Dr. Beutler and director of the Gaucher Clinic at Shaare Zedek Medical Center in Jerusalem, the largest Gaucher clinic in the world.
Beutler and Zimran reported good results with a quarter of the recommended dosaging (15–30 units per kilogram of body weight) given every other week.\textsuperscript{32} Picon compared his data with Beutler’s and Zimran’s data, “and we ended up recommending 15 units per kilogram as the initial dose, or four times less than what was recommended in the package insert, every 15 days.”

If this lower dose regimen were implemented, treatment costs would be dramatically reduced and much-needed medicines would be made more consistently available to patients, Picon reasoned. But in a pharmaceutical world of high financial stakes and vested interests, pressure came from all sides to abandon the project. During the open commentary period for the Gaucher treatment guideline, Picon was handed “15,500 pages of complaint from industry representatives and Brazilian physicians. We received letters from a major U.S. government medical research center criticizing the guideline. … I received a personal letter from someone coordinating long-term treatment for Gaucher patients. He was a lawyer and wrote that he would take our team to the International Criminal Court in The Hague.”

**Local Science: Creating a New Evidence Base**

When I first met Dr. Picon, in 2003, this dedicated, light-hearted, and amicable scientist was filled with humorous anecdotes about corporate influences on medical research and care in Brazil.\textsuperscript{33} Overwhelmed by lobbyists, threatened with lawsuits, denounced as a human rights violator, he had had firsthand experience with what he called the pharmaceutical “fourth power.” He was proud of the *Protocolos*, a large volume filled
with carefully constructed data and easy-to-read flowcharts, published by the health ministry. In all, 31 treatment guidelines for a diverse set of conditions were published. Dr. Picon conveyed his sense of frustration in implementing the protocols. The Pan American Health Organization had not published them in Spanish, as he had hoped. At the national level, implementation had also proven to be complicated—no consensus had been reached and the guidelines had no regulatory status. His challenge was still a practical one: to make practitioners in diverse worlds—medical, governmental, nongovernmental, and legal—recognize the guidelines’ scientific authority and public health value.

He decided to work locally and to find alternative pathways of scaling up. As he said, “It’s impossible to do science in a very linear way, how can I say, to put evidence into practice. To translate evidence into practice in Brazil without politics, I don’t believe this is possible.” He made a proposal to the administrators of Hospital de Clinicas: create a system of reference centers that can be used to gather data on the efficacy and validity of each of the Protocolos. The centers would become a model for administering high-cost medicines in a context of poverty and poor health. The Clinical Research Unit that he directed for the purposes of generic testing should not be left as a ruin, he argued, and could be used as an operational base for the centers. Ideally, the evidence gathered would feed into a national database, critical for influencing national drug policy and providing long-term sustainability for the project.

He proposed a Gaucher study as a pilot project, not because the financing of its treatment was particularly straining but because of the considerable international agreement over the efficacy of lower-dose treatments. It was bound to be a success story.
and could be used to galvanize support for more reference units. Indeed, controlling more widely prescribed and overused treatments (statins, for example) would be much more difficult, but that was also on his agenda. “If it is hard to obtain evidence-based medicine for a disease affecting just 470 people,” Picon reasoned, “can you imagine what is going on with other diseases affecting millions of people—where one single drug can be used for 20 diseases? at different doses? or at different prices because there are two or three or ten companies competing for the same market share? But with a disease affecting 470, it’s possible. It involves one single drug produced by one single company for one class of diseases. There is no other use for imiglucerase.”

To create the reference center, Picon and his team needed to gain control over the prescription and distribution of imiglucerase in the state. Through a hospital agreement, he partnered with the provincial health secretary of Rio Grande do Sul, Dr. Mark Terra. With the recent decentralization of health care, regional governments were responsible for drug purchasing and distribution in their states. As a public health physician, Terra was sympathetic to Picon’s point of view and was convinced of the need for such centers. Terra hired Picon as coordinator of medicinal policy for the state. Picon was now empowered to review all Gaucher patients in the state of Rio Grande do Sul whose doctors were requesting high doses of imiglucerase.

Those patients were sent to Hospital de Clinicas for medical review before further treatment could take place. For patients already being treated, according to the new protocol, “We started reducing the dose and controlling their clinical status, including changes in liver and spleen volumes, hemoglobin levels, platelet counts, and disease biomarkers. … Within six months, we reduced their doses from 60 to 30. At end of 12
months, 30 to 15. With new patients we do not start with 60, but with 50 units. In six months, and depending on the clinical response, we either increase or decrease the dose.”

As I listened to Picon speak, I could not help but ask, what about the patients? In this alternative research and treatment scheme, for example, how do researchers ever get patients to consent to a lower-dose (read: lower than standard) treatment regimen? One hears echoes of the controversy over the ethics of trials of short-course AZT treatment to halt perinatal transmission of HIV. But is this a case of ethical imperialism versus ethical relativism; are patients’ rights to health being violated? As a young teenage Gaucher patient received her infusions of imiglucerase, her mother, a nurse and former patient activist, told me of some of the reference center’s positive effects. Julia, who was born in the interior of Rio Grande do Sul, had been actively involved in organizing the judicial claims for imiglucerase for the provincial state’s Gaucher patients in the late nineties. She initially relied on an English teacher she met through a family member “to make contact with Genzyme.” She also launched a successful judicial action against the state to insure payment for the drug. “It used to be that,” she said,

“once a month, a member of our [patient] association went to the pharmacy that dispenses exceptional medication. He took all the medication and put it in a refrigerator, and we met and divided it among ourselves. Everyone had a prescribed dose. Sometimes, we ran out, and we didn’t have anymore. Sometimes I gave my daughter’s dose to another patient who had a more severe case. We shared or doctors rewrote our dosages to make sure that all of us had some. When
the reference center was established, the flow of medications became much more consistent. Once the medicines were assured, we could finally rest.

There are 12 reference centers so far. With them, Picon has created a kind of middle ground of scientific and political maneuvering—a space for negotiating the high cost of new medications that obviates triage. Patients shed their roles as neoliberal “activist patients,” a body politic which negotiates state protections and bureaucratic influence, with often tragically and unjustly varying degrees of success and failure. The “trial” is not only a hypothesis-testing instrument, but a new operative environment. Public policy vacuums that allow some and preclude others from entering health institutions as subjects of care are addressed. Patients become allies in counteracting market-induced inequalities and overprescribing physicians are monitored. As Picon puts it, “I say to physicians, the medication will come to your patients. You don’t have to go yourself to the health secretary and demand it. The flow of medication will be easier. And since you get the medication and it flows easier to you, you will give me the real life patient data. So they get better treatment and we get better information. It’s a deal.”

For Dr. Hiller, the medical geneticist, the Gaucher reference center (and future ones like it devoted to monitoring high-cost genetic therapies) breaks patients’ and doctors’ political-economic “enrollment” in the financial life cycle of a drug. In the past, company representatives kept dogging her to send patient data to the company. As she resisted, she was scientifically discredited. “Now this is our data,” she said. “And these are our patients.” In reclaiming the evidence base of high-cost genetic drug therapies,
future reference centers stake out an ethical position in the perilous demography of the
globalized trial: patients enrolled in clinical trials run in the Hospital de Clinicas will
have continued access to the drug.\textsuperscript{41} This seems like a rather simple statement, but
making it involves some interesting reversals. For example, in the context of the
reference centers, clinical trials are no longer justified as social goods in themselves—a
form of short-term health care in the absence of treatments; and “treatment naivete” is no
longer patients’ only assigned value from a clinical research perspective.\textsuperscript{42}

Indeed, the reference centers have created a repertoire of interventions aimed at
reversing the harmful dimensions of the globalized pharmaceutical trade. They are not
just about saving money, because “whatever money is saved is used to exterminate
another fire. The public health budget is just for exterminating fires.” Picon sees the
units as a domestic technology affording many uses, some not yet foreseeable.\textsuperscript{43} They
institutionalize a different understanding of the right to health (one that is less legalistic).
Call it a form of collective efficacy, enabling new partnerships between the public sector,
academic science, the courts, and patients in the governance of health.\textsuperscript{44}

“What is the other option?” Picon asks, “To not treat at all?” Among other things,
the guidelines expose the unwillingness of other low-income countries to deal with the
problem of high-cost drugs. “We looked at data from other ministries of health in South
America. Many of them are not buying imiglucerase. I was talking to an administrator
from [a neighboring country] and I asked her, ‘How can you tell me there is no Gaucher
in South America, and only in Brazil? So your patients are dying and you are not doing
anything?’”
The geography of the global pharmaceutical market is undergoing a major shift. Away from mature markets in the United States, western Europe, and Japan and toward emerging ones in Latin America, China, India, and the new eastern members of the European Union—countries with a per-capita Gross National Income of less than $20,000. Clinical trials have become an integral (if underrecognized) part of public health care infrastructures in these emerging markets. They have become social goods in themselves, enrolling people as a means of accessing state-of-the-art technology and care. But research agendas that can provide the most valid and relevant evidence base for alleviating disease burdens are by and large not being advanced. A political economy of offshored clinical research can undercut a physician-investigator’s own ability to do no harm, especially once the trial is over.

Not only are markets changing geographically but the way markets are being constituted is changing, too. Brazil’s progressive legal environment opened the way for pharmaceuticalization—a process involving “a necessary participation by the state, including in the regulation of its own withdrawal” (Sassen 2006:269). Accountability has been severely compromised, a legalistic conception of human rights has been commercially exploited, and hyperindividualized skirmishes for treatment access continue to be the order of the day. Along with the more visible and exciting new worlds of global health, Dr. Picon and his group’s work illustrates how the partnerships between the public sector, academic science, and law can reverse some of these trends. He and his colleagues are carving out highly dynamic institutional worlds and spaces of possibility,
changing the ground rules of industry-sponsored research and working toward equity in public health.

Notes

1 A blockbuster drug sells over a billion dollars annually. The phenomenon 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 (see Angell 2005).
2 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. The bulk of outsourced activities take place in the second and third phases of drug development; these phases are the most time consuming and expensive; phase three trials can involve up to 10,000 people in 10–20 countries; patient recruitment can be unpredictable, costly, and difficult.
3 Elements considered in cost-effective trial siting include local levels of unemployment, population disease profiles, morbidity and mortality rates, and per-patient trial costs and potential for future marketing of the approved drug. CROs investigate the host country’s regulatory environment. They ask whether universal access to health is in place. They assess regulatory priorities and capacities of host countries (e.g., efficacy of local ethical review boards and outlooks and regulations on placebo use). See Petryna, “Ethical Variability: Drug Development and the Globalization of Clinical Trials.” American Ethnologist, May 2005, 32(2):183-197.
4 Dr. Renata Mazur, Warsaw, Poland, 2005.
5 Dr. Jan Novak, Warsaw, Poland, 2005. In terms of CRU productivity, Latin America, he said, “is where Central-Eastern Europe was five years ago.” The terms “patient” and “subject” are used interchangeably among all of my informants.
7 Most CRO revenue (60%) comes from study monitors who are dispatched to local research sites to assure clients and regulators that clinical research is conducted according to accepted technical standards, that it complies with ethical guidelines, and that the data has integrity and is free from fraud.
8 Dr. Maria Hiller, Porto Alegre, 2005.
9 Dr. Kamran Abbasi, former editor of the British Medical Journal, recently noted that, “Fewer than 5 percent of studies in medical journals are both valid and relevant to clinicians or policy makers; in most journals it’s less than 1 percent.” British Medical Journal; “Developing European clinical research in the interest of patients and public health” 2005)
10 Dr. Andry Costa, Hospital de Clinicas, Porto Alegre, Brazil.
11 Dr. Paulo Picon, Hospital de Clinicas, Porto Alegre, Brazil.
12 An orphan disease affects “less than 200,000 persons in the U.S.” or “more than 200,000 persons in the U.S. but for which there is no reasonable expectation that the cost of developing and making available in the U.S. a drug for such disease or condition will be recovered from sales in the U.S. of such drug.” http://www.fda.gov/orphan/progovw.htm.
Under a Ministry of Health decree (under José Serra), ANVISA funded universities in Brazil to build these facilities, together with the pharmacy (schools). “We have a contract with the pharmacy college. So we do the clinical part and they do the analytical part of the project. And this is important too, we are creating technology inside the university. We are supposed to perform some of these trials in a better way than people outside the university. We want to participate in the design of the trial. For registry of regulation we do the design of the drugs. ANVISA is requiring us to demonstrate the efficacy and toxicity of old drugs. We design those trials.” Yet there was an eerie emptiness in the well-equipped and professionally-run Unit. Few patients were scheduled and few trials were actually underway—a medicine to treat rheumatoid arthritis, an insulin inhaler, a locally produced cough suppressant syrup, for example. It was not that the Unit had difficulties in patient recruitment—“We have posters advertising trials inside the hospital, announcements on TV, radio and I newspapers, and we have a good doctor referral network in place,” the Unit’s financial administrator told me. She told me that Clinicas’ high standards made the Unit less attractive to national generic firms eager for a quick monetary return in a high risk business. “In other regions, companies exploit the SUS (Sistema Único de Saúde) infrastructure and academic hospitals that do not have the strict clinical oversight we offer.” Moreover, multinationals were quick to step in the generic market and, as she puts it, “they have their own laboratories to control testing and data” (interview, 2006).

An exceptional medicine can refer to a class of medications for more clinically common disorders, like rheumatoid arthritis, that are more costly than available alternatives and offer advantages to smaller number of indications. It can also denote medications for rare and/or orphan” diseases. The budget for exceptional medicines is covered under the Portaria 380.

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inhibitors that target COX-2, an enzyme responsible for inflammation and pain. Its withdrawal from the market in 2004 was a major event in the pharmaceutical world.

Dr. Paulo Picon, Hospital de Clínicas.

The disease belongs to a class of inherited disorders known as lysosomal storage disorders. This class includes forty rare disorders linked to an inherited enzyme deficiency. The gene for the deficient enzyme was identified in 1981. NIH researchers cloned it in 1984. The FDA granted U.S. marketing approval for Ceredase, an early version enzyme replacement therapy in 1991.

Until that time, treatment for Gaucher mainly consisted of palliative measures.

http://www.shef.ac.uk/content/1/c6/01/87/47/0602FT.pdf—quote from page 5.

The maker can charge up to $200,000 a year for the average patient, years after the first version came to market, "because it can. There is no competition, patients are desperate and most insurers pay." See Anand, Geeta. Why Genzyme Can Charge So Much for Cerezyme; Why Genzyme Can Charge So Much for Cerezyme. Wall Street Journal. Nov 16, 2005: A15. The treatment remains out of bounds for most populations in developing countries, and heated debates over its high cost continue as coalitions of patient groups battle the “access crisis” in the US, the UK, and elsewhere (http://www.rarediseases.org/). The total global market of the enzyme replacement therapy is estimated to exceed US$ 1 billion. Source:


Dr. Maria Hiller, Porto Alegre, 2005.

Ernest Beutler noted that the "development of enzyme replacement therapy for Gaucher disease, […] is a triumph of translational medicine. At the same time, powerful commercial interests may have been influential in physicians adopting a high-dose rather than a low-dose treatment schedule. Moreover, the high cost of enzyme replacement therapy forces us to consider what society can afford" for very rare diseases.

The incidence of Gaucher ranges from 1 in 40 000 to 1 in 200 000. Type 1 Gaucher's disease is the non-neuronopathic adult form of the disease that is particularly common among Ashkenazi Jews, among whom the incidence is reported to be as high as 1 in 850. The prevalence of Gaucher disease in the general population is estimated to be 1 in 200,000 while in the Ashkenazi Jewish community, it is 1 in 855. It is therefore estimated that there are 35,000 to 40,000 people worldwide who have Gaucher disease. However only 3,000 patients are receiving enzyme replacement therapy and this means less than 10% of sufferers are benefiting from treatment.”


The drug’s package insert recommends an initial treatment of 30-60 units per kilogram of bodyweight (u/kg/bw), taken every other week.

I first heard about Dr. Picon and his work from Dr. Laura Bannach Jardim, one of the country’s leading young medical geneticists. She worked in the hospital’s Medical Genetics Services and had collaborated with my husband João Biehl on a study on gene-environment interactions in Machado-Joseph’s disease (Biehl 2005). With the development and marketing of orphan drugs, the internationally recognized Genetics Service was beginning to participate in clinical trials particularly for genetic therapies. While talking to her about some of the prospective trials there, Dr. Jardim told me not only about the national policy work of Dr. Picon’s team, but about how he was attempting to reshape the terms of clinical research inside the hospital.

For conditions as diverse as osteoporosis, acne, rheumatoid arthritis, asthma, acromegalia, Alzheimers, Crohn’s disease, Gaucher disease, Parkinsons disease, multiple sclerosis, schizophrenia, cystic fibrosis, hepatitis b and c, neutropenia, epilepsy, and renal transplantation.

Features of the database include detailed reports on diagnosis, treatment response, laboratory follow-up, treatment adherence, adverse effects, and dose optimization.

State health secretaries pay for the bulk of exceptional medication, with the exception of AIDS treatment, which are federally funded.
The reference center is located in the Medical Genetics Service of the hospital. Subsequently, one of Picon’s collaborators, Dr. Andry Costa, set up a reference center in the hospital’s ambulatory for monitoring statin use. He told me that for over half the 164 patients referred to the center so far, “all I was doing was taking the medication away.” When the reference center for hepatitis C was established, “We found that retreatments generally don’t work. We don’t recommend retreatment” (Picon). A group of specialists gathered to review judicial claims to Alzheimers treatments being reviewed inside the state’s general prosecutor’s office. “They analyzed 1500 claims for medicine. 6% of those claims were accepted. 94% were denied. Half of the cases denied turned out to have no Alzheimers at all. They were either misdiagnosed or they had other diseases, muscular and vascular diseases.”

See Petryna, *Life Exposed: Biological Citizens after Chernobyl* Princeton: Princeton University Press, 2002. Biological citizenship, as I show, becomes the public domain in which downward health spirals are accelerated for some, where protection is selectively promoted for others, and where the injustices of these apparently sealed destinies are increasingly known and contested politically.

Dr. Paulo Picon, Porto Alegre, 2006.

Abbasi speaks of an “evidence tyrannised” as opposed to an “evidence informed” practice, for example (2005). The reference centers address the tyranny of triage that is related to the former.

At the same they create a new kind of academic “capital” that is ostensibly free of industry-related conflicts of interests.

Some regions and countries are more attractive than others because of the abundance of what is standardly known in the industry 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” (see Petryna, 2005).

Most recently, Brazil has partnered with Cuba to produce its own peginterferon. The reference centers will be used to test the drug.

Robert Sampson, Stephen Raudenbush, and Felton Earls coined the term collective efficacy in the context of neighborhoods and violent crimes in Chicago. They define collective efficacy “as social cohesion among neighbors combined with their willingness to intervene on behalf of the common good, is linked to reduced violence.” "Neighborhoods and Violent Crime." *Science*, 15 August 1997: 918.

http://open.imshealth.com/webshop2/IMSinclude/i_article_20061204a.asp