

Institutional mistrust in the organization of pharmaceutical clinical trials

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Abstract In this paper I explore the politics of trust in the clinical testing of pharmaceuticals in the US. Specifically, I analyze trust in terms of its *institutional* manifestations in the pharmaceutical clinical trials industry. In the process of testing new drugs, pharmaceutical companies must (1) protect their proprietary information from the clinicians who conduct their studies, and (2) find a way to ensure human subjects' compliance to study protocols. Concern with these two critical issues leads drug companies to approach clinicians and research subjects with an attitude of mistrust and the desire to exert control over their activities. This orientation results in an institutionalization of *mistrust* that structures the relationships and activities required for the clinical development of new pharmaceutical products.

Keywords Clinical trials · Contract research · Drug development · Human subjects · Pharmaceutical industry · Trust

Drug development is at an all time high.¹ Many pharmaceutical companies are scrambling to add new products to their portfolios that can compensate for the loss of market share of blockbuster drugs, which are losing patent protections. In order to get new drugs to market in the US (as well as most other industrialized countries), pharmaceutical companies must first prove that these products are both safe and effective. To do so, they contract with vast numbers of

clinicians around the world to conduct clinical trials on human volunteers.

Clinical testing of new pharmaceuticals requires not only a large investment of time and money from those involved in the research enterprise, but also significant levels of *trust*. Once clinical trials begin, pharmaceutical companies lose control over proprietary information about the products they are developing and the early results of clinical testing. Thus, from the perspective of many pharmaceutical company executives, the commercial success of a product depends on careful regulation of information about the clinical performance of a new drug. In addition, it is important that research subjects comply with study protocols because the collection of accurate data ultimately determines whether pharmaceutical companies should continue the development of those drugs. Studies must, therefore, be designed in a way that leads to the most promising results possible² while encouraging subjects' compliance.

In this paper I explore the politics of trust in the clinical testing of pharmaceuticals in the US. Specifically, I analyze the *institutional* manifestations of trust in the pharmaceutical clinical trials industry. I argue that because pharmaceutical

¹ The pharmaceutical industry's investment in research and development (R&D) has grown exponentially since the 1980s. For example, in 1990, the industry's annual R&D expenditure was \$8.4 billion. In 2004, it spent nearly \$39 billion, which was a 12.6% increase from the previous year (Parexel 2005).

² Most pharmaceutical studies are placebo-control clinical trials. This type of study design is favored over studies which compare an investigational drug to other products already on the market because it is easier to prove efficacy (i.e., the new drug is better than nothing as opposed to better than an existing treatment) and these studies are considerably less expensive because they require fewer human subjects and less infrastructure (Tereskerz 2003).

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companies need to protect their proprietary information about new products from the clinicians who conduct their studies and to promote human subjects' compliance to study protocols, they approach these groups from a position of mistrust and aim to exert control over their activities. Rather than asking the question, "Can human subjects trust in the research enterprise?"—a question taken up by popular critiques of studies gone wrong,³ I ask instead—"What are the organizational implications of the pharmaceutical industry's mistrust of clinicians and human subjects?"

Methods

This paper is based on a larger project examining the US clinical trials industry.⁴ The purpose of the study was to investigate the everyday work lives of those in the industry, paying particular attention to the role and ethical conflicts that were described by informants (e.g., pharmaceutical company representatives, physicians, research coordinators, and human subject volunteers) and observed in their practices (e.g., recruitment of human subjects, informed consent processes, and study compliance). I conducted 12 months of qualitative research in the Southwestern US, consisting of interviews and observation at more than twenty for-profit research organizations in two major cities. Investigative sites (i.e., clinics conducting contract research) represented a diverse sample of organizational forms, such as private practices, dedicated research sites, and large (non-academic) hospitals. My sample also included interviews at two not-for-profit investigative sites. The majority of sites conducted studies to test the efficacy of new products that were targeting illnesses and diseases that already have safe and effective treatments on the market (e.g., allergies, asthma, high cholesterol, insomnia). Only one site consistently tested products for life-threatening conditions, such as AIDS or cancer.

The data are drawn from semi-structured interviews with 63 informants, who were clustered to get the perspective of multiple employees at individual investigative sites. The sample included 10 physician investigators, 18 research coordinators, 3 recruiters, 9 investigative site administrators, 9 pharmaceutical company employees, and

14 human subject volunteers. Interviews lasted an average of forty minutes, ranging from ten to ninety minutes. Informants were asked questions about their experiences working in the clinical trials industry, how things have changed over time, and what types of changes they would like to see in the future.

Overview of pharmaceutical contract research

Clinical research and development in the drug industry must be understood in the current political and economic context of medical neoliberalism (Fisher 2007a; forthcoming). In the US, neoliberalism is the guiding ideology behind economic policies that emphasize a reduction in social services provided by the state and an increase in the role of the private (for-profit) sector in the provision of social goods, such as health care, welfare, and education (Monahan 2006). Medical neoliberalism, in particular, is manifest in a consumer model of health characterized by an inequitable distribution of services according to who can pay for different kinds of care (Frank 2002). The pharmaceutical industry benefits from neoliberal forms of health care because un(der)insured populations in the US can be recruited as human subjects into clinical trials in exchange for limited, medical attention for the duration of studies (Fisher 2007b).⁵ In addition, many health care providers are looking for new ways to increase their revenue through a diversification of services (Gray 1993). In this climate, physicians become targeted as potential investigators on pharmaceutical studies (Pham et al. 2004). The resulting organization of clinical trials has important implications for relationships of trust in drug development.

Pharmaceutical clinical trials are characterized as 'contract research.' Unlike investigator-initiated research, those conducting pharmaceutical studies rarely have any role in defining the research questions, designing the protocols, or analyzing the results. Instead, scientists and researchers at pharmaceutical companies determine these elements of clinical trials, and clinicians are then hired to execute the protocols using their patients as subjects. Although physicians at academic medical centers and university hospitals confer legitimacy and prestige on pharmaceutical studies, the bulk of contract research is conducted in the private sector by physicians in private practices or for-profit, dedicated research centers (Bodenheimer 2000; Rettig 2000).

³ In the last decade, clinical trials have received significant attention from the mass media because of high-profile cases of studies gone awry. Examples include the death of Jesse Gelsinger in a University of Pennsylvania gene-therapy experiment (Stolberg 1999) and the near fatal injuries to six healthy subjects in a first-in-human study on an experimental product tested in London (Rosenthal 2006). See O'Neill (2002) for an analysis of the public's deficit of trust in science and medicine as a result of the media.

⁴ The research was supported by the National Institutes of Health under Ruth L. Kirschstein National Research Service Award 5F31MH070222 from the National Institute of Mental Health.

⁵ This paper concentrates primarily on Phase III clinical trials, which are designed to test the efficacy of new pharmaceutical products. For discussions of other types of studies, their organization, and the human subjects who enroll in them, see Fisher (forthcoming).

The pharmaceutical industry outsources studies to the private sector in order to speed up clinical trials (Rainville 2002). Because patent protection on their products begins at the commencement of clinical studies, it is in the interest of pharmaceutical companies to complete those studies and get their products on the market as quickly as possible (*Economist* 1998). In response to patent limits, the pharmaceutical industry often mobilizes the ‘fact’ that pharmaceutical companies lose \$1 million in potential revenues for each day drugs are delayed getting to market because of slow clinical development (CenterWatch 2003). Contracting with physicians in the private sector is seen as an effective way to speed up clinical trials because those physicians have better access to human subjects, especially private practice physicians who can recruit subjects from their own patient populations (Lader et al. 2004). Academic medical centers, in contrast, are seen as floundering at recruitment and enrollment of subjects because they do not have the same access to potential volunteers. Other delays, such as slow institutional review boards (IRBs) and contract negotiation, are also said to be associated with academic medicine (Fisher forthcoming).

Physicians too have many incentives for wanting to pursue contract research. Many physicians feel that they are losing income each year because of the rising costs of malpractice insurance and practice operating expenses and the declining rates of reimbursement from insurance companies and government programs (Tu and Ginsburg 2006). In response, many are seeking alternate ways to supplement their income. There are many options from boutique medicine and cosmetic procedures to lifestyle and nutrition counseling, but none of these provides as much income as clinical trials (Pham et al. 2004). Already enmeshed in numerous other types of relationships with the pharmaceutical industry,⁶ it is not a stretch for most physicians to begin conducting drug studies. Physicians earn an average of \$5,500 per subject enrolled and \$60,000 per study (Gray 2004). In other words, by simply doing several clinical trials on a part-time basis each year, physicians can add \$300,000 additional income to their practices.

The number of US physicians involved in clinical research has been rising steadily since the early 1990s. In less than one decade, from 1990 to 1997, the number of private-sector physicians involved in pharmaceutical studies tripled from fewer than 4,000 to nearly 12,000 (Klein and Fleischman 2002). The total number tripled again in the last ten years, with close to 35,000 private-sector physicians conducting studies in 2005 (CenterWatch 2006). Other estimates indicate that 13% of all

practicing physicians are currently conducting at least one pharmaceutical study and roughly 33% have conducted studies for the pharmaceutical industry at some point during their careers (HarrisInteractive 2004).

In order to conduct pharmaceutical studies, physicians need to invest some resources in personnel. Specifically, they need to hire (or appoint existing staff as) a clinical research coordinator to run the day-to-day clinical trials operations, such as recruiting and enrolling subjects, completing all study paperwork, and preparing for study visits made by pharmaceutical companies’ employees who monitor the activities of the clinics (Woodin 2004). Research coordinators are primarily women with backgrounds in nursing, and the industry as a whole places considerable emphasis on their interpersonal skills to build trust and rapport with human subjects to guide them through drug studies (Mueller 2001; Fisher 2006a).

Like physicians, human subjects have instrumental motives for participating in clinical trials. In some cases, such as studies to test the efficacy of new cancer therapies or other potentially life-saving treatments, people participate as human subjects because they hope for a cure or ‘magic bullet’ for their illness (Verheggen et al. 1998). In a growing number of cases, however, people participate in clinical trials as a way to access some form of medical care when they lack health insurance (Kolata and Eichenwald 1999; Fisher forthcoming). Although clinical trials are not designed to treat individuals’ conditions but to test the efficacy (or safety) of new products, human subjects nonetheless are given access to medical practitioners, diagnostic tests and procedures, and an experimental treatment (or placebo) that might alleviate their symptoms. For some people with medical conditions they cannot afford to treat, even this limited form of access to care cannot be overestimated (see Fisher 2007b). Because the vast majority of human subjects are not participating for altruistic reasons, their retention in and compliance with study protocols can be dependent on experiencing individual benefits from clinical trials (Fisher forthcoming).

In sum, the current context of US clinical trials is characterized by outsourcing of studies to physicians in the private sector who are interested in augmenting their incomes and by recruiting human subjects who have instrumental reasons to participate. On one hand, this means that the pharmaceutical industry has harnessed neoliberal conditions in its attempt to speed up the clinical development of new drugs. On the other hand, however, it also means that the system of extreme outsourcing has made the pharmaceutical industry vulnerable to more risk and uncertainty regarding the trustworthiness of the thousands of investigators it employs and the millions of human subjects those investigators recruit. In addition, unlike academic medical centers, the private

⁶ Kassirer (2005) discusses the extent to which physicians accept gifts and income from the pharmaceutical industry as a routine part of the contemporary practice of medicine.

sector has few organizational mechanisms to ensure that investigators will conduct studies rigorously and honestly. In light of this additional risk and uncertainty, trust is attenuated, making systems of control increasingly necessary.

Conceptual framework

The concept of *trust* provides a useful lens for exploring relationships among pharmaceutical companies, clinicians (i.e., physicians and research coordinators), and human subjects engaged in drug development. In the majority of scholarship on trust in medicine, the focus is primarily trained on patients' trust in their personal care providers, human subjects' trust in the researchers or institutions conducting clinical trials, and citizens' trust in their health care delivery systems (e.g., Millman 1977; Mechanic 1996; Kao et al. 1998; O'Neill 2002; Allsop 2006). Yet, for pharmaceutical clinical trials to operate effectively, clinicians must trust the pharmaceutical companies with which they are working and pharmaceutical companies must trust the clinicians and human subjects. With each of these relationships, trust is multifaceted and negotiated as individuals respond to their own and others' institutional opportunities and constraints. Several modes of trust are critical for the success of clinical development.

In the clinical trials industry as seen elsewhere, trust is necessary to ensure effective cooperation of all relevant actors and organizations (see Luhmann 1979; La Porta et al. 1997). One way of understanding this dynamic is to distinguish between how trust is constituted differently in individuals and institutions. This difference in types of trust is important because both levels—the individual and institutional—can shape the other, but each have unique implications, particularly if trust is misplaced (O'Neill 2002). Specifically, trust in individuals may overemphasize those actors' intentions and motives while obscuring the effects of how institutions structure (and limit) that trust (Shapiro 1987). For example, physicians conducting drug trials may indeed have the best interest of human subjects in mind, but nonetheless they have only limited jurisdiction over decision-making regarding subjects' participation. Thus, subjects' trust in those physicians may give them a false sense of confidence that their well-being is appropriately safeguarded. Examining trust at the level of individuals can ignore the myriad constraints that are placed on the range of individual actions and choices. In other words, trust does not occur free from social, political, and economic contexts; it must be understood in terms of power and control (Knights et al. 2001; Mizrachi et al. 2007). Some examples will make more concrete the

distinction between individual and institutional levels of trust.

Whereas patients' trust in contemporary medicine is a product of the cumulative histories of the professionalization of medicine (Starr 1982) and the regulation of the pharmaceutical industry (Abraham 1995; Hiltz 2003), clinical trials, especially those conducted within standard medical care settings such as private practices, create challenges to human subjects' trust. Because there are no historical models for trust in research settings (and in fact, there is ample evidence for a model of *distrust* in research⁷), the investigator-subject relationship in the clinic must borrow from a paradigm of care (Mueller 1997). This care model, however, is extremely problematic in clinical trials. Not only can trust based on 'care' lead to unrealistic expectations about the benefits of research (e.g., Appelbaum and Lidz 2008), it also leads to misunderstandings about clinical research more generally, including the role of human subjects in pharmaceutical drug development (Fisher 2006b). Moreover, the trust patients and human subjects have in physicians can be eroded by disclosures about physicians' financial conflicts of interest. In fact, this concern has led to the use of euphemisms in informed consent forms to mask the extent of financial arrangements between physicians and pharmaceutical companies (Zink 2004).

Human subjects are not alone in negotiating relationships of trust. Physicians' trust in pharmaceutical companies is equally important to the research enterprise. Specifically, physicians must trust that pharmaceutical companies are designing clinical trials with scientific rigor, are not exposing human subjects to undue harm, and are producing products that will be better for future patients than those currently on the market. As contract researchers, physicians are commissioned to follow study protocols, not to have scientific insights or ethical misgivings about the studies. In fact, most physicians distinguish themselves from their academic counterparts and pharmaceutical companies' scientists by acknowledging that they do not understand the science of pharmacology and by emphasizing that their expertise is limited to the clinic. While physicians do develop personal relationships with individuals at specific pharmaceutical companies, the type of trust that they need in order to participate in the clinical trials industry is largely institutional. This means that physicians must trust the pharmaceutical industry *as a whole* to develop investigational products in such a way

⁷ The most notable case of abuse to human subjects is the US government funded Tuskegee syphilis study, in which enrolled African American men were denied treatment for the disease for decades (Jones 1981; Reverby 2000).

that these new drugs or devices will be safe and appropriate for study in humans.

At the same time, in order to attain clinical results about their products, pharmaceutical companies must trust that clinicians contracted to do the research will collect data honestly and thoroughly and that human subjects will be compliant. Research malfeasance does occur in pharmaceutical clinical trials; some clinics have been discovered to have grossly falsified subjects' charts and data (Eichenwald and Kolata 1999). Unlike human subjects' trust in physicians or even physicians' trust in the pharmaceutical industry, pharmaceutical companies do not exhibit tacit trust in physicians and human subjects. Instead, the pharmaceutical industry regulates its relationships with physicians and their staff through legally-binding contracts and a cultivation of 'audit culture.'⁸ As with other industries, audit is seen as a mechanism for *enabling* trustworthiness through monitoring and oversight (Skinner and Spira 2003). Specifically, each clinic conducting drug studies is scrutinized by pharmaceutical company employees. Because they oversee clinical trials by analyzing all data collected at the clinics, these employees—aptly referred to as 'monitors'—symbolize the institutionalization of trust between the companies and clinics. In other words, the industry presumes that formalized oversight of clinics' activities is necessary to establish the structure in which clinics *can* be trusted *because* they are monitored.

Thus, trust operates simultaneously on two levels: the individual and institutional. Problems can arise when human subjects locate their trust—or mistrust—in physicians instead of the pharmaceutical industry or when physicians trust that pharmaceutical companies are making decisions about study protocols based on ideals of science rather than financial factors. In these cases, both groups' trust is misplaced. In contrast, the pharmaceutical industry does not seem to privilege trust in individuals over institutions. To the contrary, the mode for pharmaceutical companies is an institutional model of *mistrust* of human subjects and clinicians conducting studies.

Pharmaceutical companies' mistrust in and control over clinicians and human subjects

Recent work in the social sciences has examined the dialectical relationship between trust and control (e.g., Knights et al. 2001; McEvily et al. 2003; Skinner and Spira 2003; Mizrahi et al. 2007). Whereas earlier scholars envisioned trust and control as mutually exclusive properties, current empirical analyses indicate that power relations make the two interdependent. As Knights et al. (2001) state, "The

production of trust often relies on, and reproduces, relations of control because control also becomes problematic in the absence of trust" (312). Given the complexity of organizations today, relationships within and between companies can no longer be premised simply on personal connections, which is one business model that can provide the basis for trust (Granovetter 1985). In fact, Shapiro (1987) argues that industries must often create a 'social organization of distrust',⁹ or "a supporting social-control framework of procedural norms, organizational forms, and social-control specialists, which institutionalize distrust" (635).¹⁰ This organizational strategy can be understood as a way to manage risk and uncertainty through a highly controlled and controlling mode of trust (Seligman 1998).

In the pharmaceutical industry, mistrust¹¹ is institutionalized in two sets of relationships: (1) pharmaceutical companies' relationships with clinicians conducting clinical trials and (2) pharmaceutical companies' relationships with human subjects enrolled in studies. Institutional mistrust is explicit in policies and procedures that limit the degree to which clinicians can use companies' proprietary information and in clinical protocols designed to increase the compliance of human subjects during the studies. In other words, institutional mistrust is not simply a property that characterizes the pharmaceutical industry's *perceptions* of clinicians and subjects, but is instead a force that shapes the *organization* of clinical trials work and study participation.

Relationship between pharmaceutical companies and clinicians

The process of drug development, like many other entrepreneurial activities (La Porta et al. 1997), requires cooperation from multiple organizations to be successful. Trust is seen as a critical mechanism for structuring relationships and mobilizing actors to contribute to the collective goal (McEvily et al. 2003). Yet, pharmaceutical companies' relationships with clinicians are forged within the broader context of profit margins and competition with *other* pharmaceutical companies.¹² As an employee of a pharmaceutical company explained,

⁹ Sztompka (1998) similarly argues that democracies are founded on an 'institutionalization of distrust' that enables citizens to trust.

¹⁰ Shapiro (1987) also describes how the social organization of distrust creates new markets for 'trust production.' This seems to be particularly true in the clinical trials industry given the development of ancillary companies that share risk with pharmaceutical companies by taking on some of the control functions in drug development.

¹¹ Shapiro (1987) uses the term 'distrust' in her writing. I prefer the term 'mistrust' because it implies a lack of trust, rather than the more explicit suspicion and doubt implied in the former.

¹² Anderson et al. (2007) provide a nuanced exploration of the effects of competition on science, especially in terms of research ethics.

⁸ For more on audit culture, see Strathern (2000).

[In the clinical development of products], this is absolutely ‘time is money.’ Because you’re working on a drug and there’s probably three or four other companies that are working on it, and the first to market is the one that’s going to make it. I mean [if you’re not first,] you’re just going to be a ‘me-too’ drug.¹³

Because competition among pharmaceutical companies is fierce and because companies need to get new products to market as quickly as possible, there is considerable desire from companies for control. One important domain of control that companies seek concerns secrecy about the molecular structures of their products, including their mechanisms of action in the body. Unlike many other industries, however, there is not a lot of opportunity for pharmaceutical companies to keep their products under wraps until they are unveiled to the public. Instead, pharmaceutical companies must submit vast amounts of data to the US Food and Drug Administration (FDA) to gain approval for testing those products in humans, provide significant information to physicians who are considering becoming investigators through contract research arrangements, and craft informed consent forms for human subjects that describe preliminary findings about the products from prior animal and human testing.¹⁴ With this amount of information in circulation, it is no wonder that pharmaceutical companies seek to control the extent to which their data can be released beyond these groups.

In general, pharmaceutical companies do not trust the clinicians whom they employ as contract researchers. This is not to say that all individual physicians and research coordinators are viewed as inherently untrustworthy; rather contract research is institutionalized in such a way to restrict wrongdoing in the research protocols or leaking of proprietary information. This manifests at all stages of interactions between companies and clinicians: before contracts to conduct studies are issued, during the process of executing those studies, and after the data have been collected and the studies concluded. In fact, several pharmaceutical company representatives commented to me that their companies have a culture of paranoia regarding the

release of proprietary information, which can be oppressive for employees.¹⁵

For example, before physicians are provided with any information about studies that they are being solicited to conduct, pharmaceutical companies ask them to sign a ‘confidential disclosure agreement’ that dictates the terms of physicians’ use of proprietary information about the product under development.¹⁶ In addition to signing such an agreement to review study protocols, pharmaceutical companies also tend to limit the amount of time during which physicians can consider whether they are interested in conducting the study. In many cases, they are only given a matter of days to make a decision.

Although pharmaceutical companies are generally open to contracting with physicians who are relatively inexperienced at conducting pharmaceutical clinical trials, they are interested nonetheless in identifying clinicians who will perform well during the studies. Recall that the main purpose of outsourcing studies to the private sector is to speed up how quickly studies can be completed. Pharmaceutical companies want to contract with clinics that have available patients who match the criteria defined by the study protocols and that are committed to recruiting and enrolling those patients into studies. While it may be difficult to determine which private practices may be better than others, pharmaceutical companies are especially eager to work with physicians who have set up full time clinical trial operations. A pharmaceutical company employee described the difference,

[With the small private] practices, [they say] “You know, if the clinical trial part doesn’t work, well, we’ll just go back to being full-time private practice.” ... [On the other hand], [with the full-time sites] that’s their business and if they don’t do what they’re supposed to do, they’re not going to be around. I mean that’s what these people are doing for a living, so you trust that they’re able to do what needs to be done.

In other words, pharmaceutical companies find that clinics that have more of a financial stake in the success of their clinical trials are more apt to succeed and, hence, are more trustworthy. Companies can depend on them to conduct studies well and meet their timelines because those clinics will be seeking future business contracts.

At the same time, however, because clinical trials can be such a profitable enterprise for clinics, pharmaceutical

¹³ In one important respect, all drugs that compete in a certain class are ‘me-too’ drugs. This is because they are each trying to get the most market share whether they were first, second, or even tenth to become available by prescription. See Angell (2004) for more discussion on the politics of me-too drugs in pharmaceutical R&D and in US health care.

¹⁴ In addition, many pharmaceutical companies choose to outsource the management of clinical trials to independent companies called contract research organizations (CROs). In those cases, proprietary information is then shared with those CRO employees assigned to the trials. For more information on CROs, see Mirowski and Van Horn (2005) and Fisher (forthcoming).

¹⁵ In fact, one informant asked me not to sign in when I met her in the lobby of her office building because she preferred that there be no record of my visit to the company. We then proceeded to a nearby restaurant so that she was not questioned by any of her supervisors about the interview.

¹⁶ Seligman (1998) discusses how contracts are a result of the changing character of trust in the modern era.

companies have concerns that clinicians may not conduct studies honestly and according to their protocols. The monitoring of those sites through employees who travel to each clinic every six weeks (on average) is an institutionalized mechanism to help ensure that clinicians will perform studies honestly and according to protocols. Monitors admit that fraud is rare, but that they all know about cases where it has happened. Performing study visits enables them to have a visual check of all data and the conduct of the studies. A monitor explained her job,

We're taught to learn how to look at data that's given to us and look for patterns of fraud, and to make sure there are indeed patients, that it looks like patients are going in and out [of the clinic], and the data looks correct.

In practice, however, monitors' job extends beyond the function of detecting research fraud. The vast majority of monitors' time is spent aiding clinicians to better execute protocols and document studies (Woodin and Schneider 2003). This also contributes to the trustworthiness of the data produced because any unintentional errors that clinicians make in the process of conducting studies can be corrected. Thus, monitoring enables trustworthiness even as it reinforces mistrust (Skinner and Spira 2003).

A final element of pharmaceutical companies' mistrust of clinics conducting studies is found in the reporting of results to clinicians after the clinical trials have been terminated. In general, there is little communication between companies and clinics about the outcome of testing.¹⁷ Oftentimes, clinicians are left to speculate about the fate of an investigational product based on the available evidence they received. For instance, when clinics involved in early human testing of a new drug are asked to conduct further studies on that product with the same company, they reasonably interpret the results of the first study as generally promising. Another common scenario is for clinicians to find out about the products when they are marketed to the general public. For example, a site manager said,

More often than not, [you find out the results of the clinical trials because] you see a commercial on TV and say, "Oh, that sounds like the drug we tested!" We don't know the name oftentimes when we're doing the research. Actually, it doesn't have a name yet, it's usually going by a chemical name, and then the marketing people get a hold of it and give it a name. So we say, "Oh, we did that study" because they'll say what the generic name is.

¹⁷ This is also true for the human subjects who participate in the studies. Subjects rarely receive information about the outcome of clinical trials, and when they do, the information comes informally from clinicians, not officially from pharmaceutical companies.

Although most clinicians are very interested in finding out the results of the trials on which they worked, pharmaceutical companies believe that it is better for them not communicate study results except through carefully controlled mediums, such as advertising, authorized publications, and company websites. A pharmaceutical company project manager who orchestrates the clinical trials of one product under development explained,

[We don't share the information because what the] pharmaceutical companies have to guard against is if the results are sent to a doctor, the doctor might write a paper and publish. That can't happen until you're completely through your NDA [New Drug Application with the FDA]. So that may have something to do with why it's so hard [for sites] to get results from a sponsor.

The threat of clinicians publishing their own interpretation of clinical trial results is more complicated than it may at first appear. Because clinicians tend to work with multiple pharmaceutical companies, they often gain experience working with investigational drugs that are chemically quite similar ('me-too' drugs) that are being developed simultaneously by several companies. In theory, clinicians could publish papers describing their experiences with these different drugs to speculate on the advantages or disadvantages of one over others. In practice, however, it is unclear that many private-sector clinicians actually have any interest in writing reports about clinical trial results.¹⁸ Nonetheless, contract researchers' experiences—as non-systematic as they are—are often the only clinical evidence of how drugs compare to each other because most companies do not design comparative studies and the FDA does not require comparison of most new drugs against other drugs, only against placebos.

Relationship between pharmaceutical companies and human subjects

Just as mistrust shapes the drug industry's relationships with clinicians, pharmaceutical companies' design clinical trial protocols with the implicit assumption that human subjects cannot be trusted to be compliant and complete studies without the proper structure and control. This can be observed by frequent study visits, formal mechanisms to count the pills human subjects are given and consume, and

¹⁸ None of the clinicians with whom I spoke ever discussed writing papers to be published. Two things seem to be taken for granted. First, publishing is the kind of activity reserved for academic physicians and their teams. Second, the pharmaceutical industry hires ghostwriters to put together papers for publication (see Sismondo 2007). As a result, physicians dismissed writing articles as an activity that was simply not in their purview.

electronic or automatic data capture systems to track subjects' symptoms. Furthermore, the human subjects who make up pharmaceutical clinical trials are recruited from patient populations that pharmaceutical companies hope will have more incentive to be compliant and to complete studies.

Most clinical trials require frequent study visits, which subjects must attend within a set window or risk being removed from studies. On one hand, study visits are medical; human subjects must be monitored through diagnostic tests over the course of studies to ensure that their well-being is safeguarded. Yet, on the other, many of these visits serve to remind subjects about the importance of compliance *out of* the clinic by establishing a structured mode of compliance *within* the clinic.¹⁹ Research coordinators discuss the explicit role they play in educating subjects to be compliant: "Our job is really to educate our volunteers about their responsibility *to us*." Specifically, reviewing informed consent forms with subjects at each study visit provides a clear reminder about human subjects' responsibilities to pharmaceutical companies within clinical trials. In addition, study visits allow clinicians to assess subjects' compliance and to get them to change their behaviors if they have not been strictly following the study protocols. For example, a coordinator explained that study visits provide her the opportunity to identify "the patients [subjects] you want to spend a little more extra time with because you need to re-educate them about their responsibility as a patient that enters a clinical trial."

A major part of human subjects' commitment to clinical trials is to consume the investigational drugs (or placebos) provided during the study. Just as in standard medical care, there are many reasons why subjects are less than perfectly compliant with dosing schedules and regimens. This 'normal' non-compliance is not acceptable, however, in the context of clinical trials because pharmaceutical companies are counting on subjects' consuming their products to produce results about new drugs' effectiveness. The assumption is that when subjects strictly follow the protocols, the companies are more likely to see positive results from their products compared with when subjects are less compliant.

As a result, pharmaceutical companies mandate drug counts to keep track of how well subjects' are following the protocols. In other words, subjects are given a specific number of pills to take home, they are asked to bring those pills with them to their next study visit, and research

coordinators count the remaining pills to assess whether subjects are taking the pills as often as directed. A coordinator described the technique,

You'll come up with maybe an odd count of pills when they come in for their next visit, and when you question them, they'll come up with a decent excuse or something. But when it happens repeatedly... you pretty much get a feeling [that they're non-compliant], and then you start questioning it a little further.

While the strategy is motivated by pharmaceutical companies' mistrust, pill counting is hardly a fail-safe way of evaluating subjects' compliance.²⁰ A coordinator said, "Then you'll find out later on where patients will take the medication home, they'll pop the pills through the casing every night and throw them out. They never really take them, and *you* don't know that." Pill counting is only one small way to structure subjects' compliance.

A more important mechanism to ensure and measure compliance in studies is the move to electronic data collection systems. Unlike standard medical care, human subjects must take a much more active role as participants in clinical trials.²¹ Subjects are not just asked to take products, but they also must report on their progress with those products. In order to get data from the experiences of human subjects on their investigational products, pharmaceutical companies need to encourage subjects to report accurately and fully all symptoms (or the alleviation of prior symptoms) over the course of the drug study. In the past, much of this data collection was done through paper-based 'symptom diaries.' Companies found, however, that there was no way to track *when* subjects actually filled out the forms. A coordinator reflected,

In a lot of the studies, the patients [subjects] have to keep daily diary logs. [When these are paper-based], a lot of [subjects] fill them in, in the parking lot a half hour before their visit. So of course, their answers are going to be completely biased.

In order to prevent subjects' from neglecting their diaries, the pharmaceutical industry has moved toward the use of electronic data capture that can time- and date-stamp

¹⁹ Some clinical trials include in-patient study protocols in which human subjects are confined to the clinic for the length of the study. These are most common as part of first-in-human or other early clinical studies. In-patient studies are a particularly important trial design when subjects must follow strict dosing schedules, require many medical procedures, and/or consume set diets (e.g. high-fat or high-calorie) that are mandated by the FDA.

²⁰ 'Smart' pill bottles and blister packs have now been introduced to clinical trials in order to more precisely monitor subjects' compliance (Goldfarb 2007). These new technologies are designed to collect data on when bottles are opened or pills are pushed out of their packaging. Currently, these technologies are not widely integrated into clinical studies, but pharmaceutical companies may start adopting them in the near future.

²¹ Some within the industry argue that an active role is empowering for subjects, but this view neglects the myriad ways in which the context of human subjects' decision-making about trial participation and the structure of study protocols actually limits subjects' authority over their bodies and well-being (Fisher and Ronald forthcoming).

subjects' responses. A coordinator explained one such system used by a study:

I have one where a participant has to call every night between 8 and midnight and talk to a machine, it's called a 'voice activated response system,' because that's how they're capturing their data. It asks: "How well did you sleep last night? Did you take your medication? What time did you go to bed? How long did it take you to fall asleep? How many times did you wake up?" There are thirteen questions that they have to answer. And if they don't call at least 10 times out of 14 days, we have to kick them out of the study because the pharmaceutical companies are losing their data.

In this case, not only does the system monitor subjects' experiences on the trial, it penalizes them if they do not use it by threatening to terminate their participation in the study if they are not compliant with the reporting tool.

In other cases, human subjects are given PDAs as electronic symptom diaries. Although their data are generally not immediately transmitted to pharmaceutical companies, the date and time of each entry is recorded as part of the subjects' records. A problem occurs, however, when subjects lose their PDAs. According to a coordinator who conducts studies that require subjects to monitor the frequency of urination with a PDA, loss of the device is a much bigger problem than with paper-based diaries. Because these studies are structured for subjects to take those technologies with them, there is a risk that subjects can forget the device in public restrooms. As the coordinator explained, "Can you lose your bladder diary somewhere? Yeah... I've had patients that have called up and said, I lost my diary. And then of course like the sponsor [pharmaceutical company] really goes ballistic." In other words, pharmaceutical companies have to balance the convenience of PDA-based data entry systems with the risk that those devices (and hence, their data) could get lost.

Coordinators report that electronic devices have increased compliance even when human subjects are not familiar with those technologies.²² Because these digital technologies create a formal structure in which human subjects must comply or their non-compliance will be recorded, many subjects are much more conscientious about completing the symptom diaries. By instituting more sophisticated data collection techniques, pharmaceutical companies encourage human subjects to be more compliant

(especially when they risk being discontinued from the study if they are found to be non-compliant).

Finally, the patient populations themselves that are recruited into pharmaceutical clinical trials provide one more means for companies to enroll 'trustworthy' subjects in their studies. By locating clinical trials within disparate communities across the country (and world), pharmaceutical companies aim to attract certain populations. The decentralized structure for conducting studies allows for pharmaceutical companies to capitalize on populations that will have reason to be compliant with protocols and complete studies. One such population consists of the patients within the private practices that are conducting clinical trials. Because those patients already have rapport with clinicians, they are seen as more likely to be compliant and easier to retain in studies. According to one coordinator,

Usually the private patients [are better subjects because] they know us, they know the doctors. They're usually more willing and they trust us because they know that we wouldn't put them in anything that would be detrimental to their health.

Nonetheless, because this group can continue with or revert back to standard medical care, private practice patients may be less motivated to continue in studies when they are unhappy with whatever results they are experiencing from investigational drugs (or placebos). They may opt to go back to the prescription medications that had worked well for them before they began the studies.

More importantly, clinical trial participation offers incentives for many potential human subjects who are not getting other treatments for their conditions. Most studies do not charge subjects or insurance companies for the cost of study visits, diagnostic tests, medical procedures, or investigational drugs. For many human subjects without any or adequate health insurance, participation in clinical trials may be perceived as the only way for them to access the medical establishment. As a pharmaceutical company employee stated,

People are just not getting *care* anymore. I don't know what we're going to do with things going the way they're going... Research is the only care people will get. It could be because that's the only place that they're willing to pay. Pharmaceutical companies are willing to pay, so patient-subjects get the care.

In general, pharmaceutical companies maintain their mistrust in human subjects, assuming that they are prone to be non-compliant and that studies should contain formal mechanisms, like electronic data capture, for encouraging subjects to follow the protocols. Larger problems with the health care delivery system in the US, such as unequal access to care, also creates populations who may be more

²² A coordinator said, "I thought the older people would not do well, having to put electronic data into a Palm Pilot, but they have surprised us, haven't they? We were so scared to give a 69-year-old a Palm Pilot and try to educate them on how to do it, but they're the ones that are on time for their appointments and use the Palm Pilots perfectly."

trustworthy human subjects because they do not have many or any alternative means to receive treatments for illnesses that need medical attention. Thus, the pharmaceutical industry is banking on making human subjects more trustworthy clinical trial participants through both the structure of the study protocols and the offering of a ‘free’ alternative for obtaining health care.

Conclusion

Whereas most attention to trust in human subjects research examines the relationships among *individuals*, I argue that *institutional* forms of trust and mistrust play a key role in shaping clinical research. This is particularly true in pharmaceutical drug development. The outsourcing of studies to thousands of clinicians in diverse locations within the US and around the world eliminates the possibility for direct personal contact amongst all the individuals involved in clinical research. Because the individuals writing the study protocols are not the ones conducting them and because most pharmaceutical company employees have very limited interactions with clinicians and none with human subjects, it is no surprise that a model of trust based on individualized relationships is untenable.

Moreover, the neoliberal health care system in the US creates an incentive for physicians and human subjects to participate in clinical trials for their own instrumental motives (i.e., financial gain for physicians and access to the medical establishment for subjects). Because common, socially-oriented incentives for involvement in clinical trials do not exist, pharmaceutical companies must develop structures that control the behavior of clinicians and human subjects.

Some could argue that these practices by pharmaceutical companies are not instances of mistrust but merely effects of a larger regulatory context, the desire to hold proprietary information secret, or the ‘neutral,’ ‘disinterested’ requirements of science. My data suggest otherwise. In the first case, the practices of the pharmaceutical industry exceed the demands of regulation. The organization of monitoring studies is considerably more detailed and complex than what the regulation requires. Likewise, the pharmaceutical industry is not succeeding in keeping their proprietary information secret in so much as they are controlling the use of that information in very particular ways. Finally, science itself can be seen as political in that it operates within a similar social organization of distrust that dictates the norms and practices of good science (Zuckerman 1977; Anderson et al. 2007).

It should be noted that my framing of the organization of clinical trials is not a condemnation of the pharmaceutical industry. I am not making a normative claim that

companies *should* trust clinicians or subjects. Instead, I am making an empirical argument about the ways in which the pharmaceutical industry manages risk and trust through specific organizational structures and practices. In order to understand the ethics of trust in pharmaceutical clinical trials—including the ways trust reflects arrangements of power—one must examine the institutions that structure, encourage, and constrain trust. In an era in which human subjects research is big business, a focus on trust solely within the clinician-subject dyad is empirically deficient and ethically dangerous.

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