Introduction

"Your Health Is Your Wealth"

Imagine you've been asked to test the safety and tolerability of an experimental drug. To do so, you will consume either the drug or a placebo—an inert sugar pill—in a Phase I clinical trial.[1] You've been informed about the risks of the drug, and you've also been told there are no medical benefits of taking it. The only direct benefit to you of participating is that you will receive up to $5,175 for completing the study.[2] If you choose to enroll in the clinical trial, you must spend 20 consecutive nights literally locked in a research facility and then return for a final outpatient study visit. You won't be able to leave the facility once you check in unless you withdraw from the study. No one can visit you at the facility, and you will share a bedroom with several strangers. You will be told what to eat, when to eat, and when to sleep. You must submit to over 50 blood draws and other less invasive medical procedures and physical exams.

The reason you've been asked to participate in this clinical trial is that you've been deemed healthy. You're under 55 years of age, have a body mass index (BMI) categorizing you as healthy, have normal blood pressure, kidneys and a liver that are functioning well, and you do not use nicotine products or illicit drugs. You might think of the clinical trial as an opportunity to leverage your health as a type of commodity—income for you in exchange for data for a pharmaceutical company. But before you decide if you will participate, perhaps you need to know more.

What Are Phase I Trials?

Pharmaceutical research and development (R&D) progresses through multiple stages before a product is released to national markets.[3] Beginning with so-called bench science in laboratories and proceeding to safety and efficacy testing on nonhuman animals, the earliest stages of R&D aim to identify molecular entities that have the potential to treat or cure disease. Only when researchers deem those investigational compounds to be promising and reasonably safe can clinical testing—studies that enroll

human subjects—begin. According to current industry norms (and regulated by national agencies such as the US Food and Drug Administration [FDA]), the testing of new pharmaceuticals in humans must begin with Phase I clinical trials to help establish the safety profiles of investigational drugs and set dose levels for future studies. Most, but not all, Phase I trials use healthy volunteers as research participants. Phase II studies enroll a small number of patients to gather additional safety data and provide preliminary evidence about the investigational drug's efficacy. In a sense, Phase II studies are like a proof-of-concept trial, allowing companies to assess whether the product is worth a larger-scale investment of time and resources. For those drugs that show sufficient promise, Phase III studies are designed to provide evidence of the product's efficacy by enrolling hundreds or thousands of patients as research participants.[4] With results from all three clinical trial phases, pharmaceutical companies can then seek approval to market their drugs. If approved, the FDA—or other countries' regulatory bodies—might also require post-marketing surveillance studies, called Phase IV trials, in order to have more safety or efficacy data about the product even as it is widely prescribed to patients. Given the complexity of the drug development process, a clinical trials industry consisting of companies that assist in the design, management, and analysis of these trials now exists and profits from pharmaceutical companies' efforts to get new drugs to market as quickly as possible (Fisher 2009; Mirowski 2011; Petryna 2009).[5]

This book focuses exclusively on Phase I clinical trials conducted on healthy volunteers.[6] In most therapeutic areas, healthy volunteers are the preferred research participants for these safety studies; however, terminally ill or disease-affected patients are also sometimes used. In lay terms, Phase I trials measure the bodily changes, or "adverse events" (AEs), that occur when research participants are given an investigational drug. Starting with small doses and increasing the number of milligrams over the course of a trial, investigators assess the tolerability of the drug as they seek to find a therapeutic dose without burdensome side effects. After administering an investigational drug to participants, researchers document all physiological changes that are captured by medical procedures as well as participants' self-reported symptoms. These changes can and do include a range of experiences that researchers suspect are not caused by the investigational drug, which is why the preferred term

is "adverse event" rather than "adverse effect." AEs such as headaches or stomach upset are common occurrences, and they prove ambiguous with regard to causation. Researchers must then adjudicate, along with the pharmaceutical company sponsoring the trial, which adverse *events* are or could be actual adverse drug *effects*.

Given the goals of Phase I trials, the advantage of enrolling healthy participants over patients is three-fold. First, there is less ambiguity in the interpretation of AEs when there are no underlying illnesses that create symptoms in participants. Second, the risk of serious complications is diminished when participants have normal kidney and liver function and can withstand temporary impairment to these organs. Finally, and arguably most important, the recruitment of healthy volunteers tends to be very rapid, especially compared to studies requiring ill or diseased participants (e.g., Battelle 2015; Fisher 2007), and efficient recruitment helps to speed successful products through the development pipeline and onto the market.

Phase I trials are distinct from later-phase studies (i.e., Phase II, III, and IV trials) not only in the enrollment of healthy volunteers but also in the design of the study protocols. Phase I studies tend to be conducted in residential clinics that specialize in this type of research.[7] These studies are also shorter in length, lasting only several days or weeks compared to several months or years for later-phase trials, and they generally require participants to consent to a clinic confinement for some part of, if not the entire, study. The confinement period enables control of participants' diet and frequent collection of data about the investigational drugs, primarily through electrocardiograms (referred to as ECGs or EKGs) and blood and urine collection. For example, on the day a drug is administered, it is not unusual for the protocol to require ten or more blood draws during a 24-hour period. The confinement also helps to ensure that participants are reasonably safe during the study because the research staff can monitor them and intervene should any serious adverse event occur.

Will You Participate in the Trial?

As you consider whether to enroll, you might turn to the informed consent form for specific information about the study. You likely want to know what drug is being tested, what medical condition the drug is being developed to

treat, and whether it is currently available on the market in any other form. You are probably also curious about the risks, notably what the drug's side effects are expected to be. The study you are considering includes in its consent form a list of potential risks that you might recognize as fairly typical for Phase I trials. They range from mild to severe: headaches, diarrhea, constipation, nausea, dizziness, skin reactions, allergic reactions, anemia, depression, liver problems, impaired kidney function, seizures, severe arrhythmias, and death. If you ask, the research staff will be quick to reassure you that no one in previous groups of the trial has experienced any severe or life-threatening reactions.

To make your decision, you might want to know more about the logistics of the study: what the specific dates of the confinement period are, what amenities the facility has, and what clinical personnel will be available to you. Most facilities are impeccably clean (though sometimes drab) and have professional and friendly research staff (though sometimes not equally skilled in venipuncture). The food may leave something to be desired, but all your meals will be prepared for you while you're there. There are also large-screen TVs, movies, video game consoles, computers, pool tables, books, and Wi-Fi to help occupy you during the downtime, which will be considerable during those 20 days in the clinic. Think of it as a vacation, albeit a strange one. Or if you'd prefer, think of it as a job because the countless restrictions—no caffeine, no exercise, no recreational eating—and the detailed regimen—especially the personalized daily schedule that specifies to the minute your "events" such as drug dosing, blood draws, and meals—will certainly remind you that your body is not completely your own while you are there.

You could be hesitant to enroll based on your assumptions about who else might be participating as healthy volunteers. You might wonder how similar to you the other participants will be. Perhaps you expect that Phase I trials are filled with students. You imagine they are young people transitioning to adulthood who need the financial boost that the study compensation provides, but this assumption would be incorrect. While students were historically the primary source of research participants at universities (Prescott 2002), they are not the usual pool of Phase I healthy volunteers.

Who Participates in Phase I Trials?

Men and racial minorities are the predominant Phase I trial participants. Study protocols frequently place restrictions on the participation

of women of "childbearing potential," often excluding those who take hormonal contraceptives or requiring them to be surgically sterile (Corrigan 2002). Thus, the percentage of men is typically around 65–70 percent overall and can be 100 percent for particular studies (Chen et al. 2018). Phase I safety protocols provide an explanation for women's underrepresentation in these studies, but there is no parallel scientific reason for the *over*representation of minorities. Nonetheless, relative to the US population as a whole, blacks and Hispanics make up a disproportionate number of healthy volunteers, with roughly 60 percent coming from these two groups (Fisher and Kalbaugh 2011). This trend runs counter to national concerns about the underrepresentation of these groups in later-phase research (see Epstein 2007) and makes Phase I trials a key place to study minorities' participation in medical research.

To recruit healthy volunteers, clinics advertise by highlighting the financial compensation for participation. In general, the amount a study pays is tied to the length of the confinement, with an average rate of $200 to $250 per night dictating the total payment. Because all research participants have the right to withdraw from a study at any point for any reason, clinics incentivize healthy volunteers through so-called completion bonuses to finish the study. This means that participants who withdraw from a Phase I trial receive a pro-rated amount of $100 to $125 per night instead of the full $200 to $250, and the difference in total compensation is reserved for those who finish the trial. In other words, the compensation is used as both a recruitment and a retention tool.

Because the monetary compensation is the primary, if not sole, motivator to enroll as a healthy volunteer, the catalyst for Phase I participation is often financial need. Such need can be singular and related to a specific bill or purchase, or it can be the product of persistent economic insecurity. Just as adverse events occur within studies, so, too, they occur in participants' everyday lives and affect their financial status. Unemployment, bad credit, debt, and incarceration are adverse events that many in the US experience but that disproportionally affect men of color. In this context, clinical trials can be an attractive option for counteracting any temporary or sustained challenges to one's financial situation. Moreover, healthy individuals can enroll repeatedly in Phase I trials and gain a revenue stream to combat or hold at bay adverse life events when they are triggered.

As a result, the vast majority of healthy volunteers participate *serially* in clinical trials (Elliott 2008; Tishler and Bartholomae 2003), and those who enroll frequently can even be thought of as "professional" participants who earn their living in this way (Abadie 2010). Although these individuals depend financially on such studies, their ability to participate cannot be taken for granted. Some first-time participants underestimate the difficulty of getting into these studies, but the "veterans" know that qualifying for Phase I trials is not always easy. First, the availability of studies ebbs and flows, with some clinics seemingly having very few trials for weeks or months on end, followed by a wave of new studies. Second, ensuring that one's body chemistry and vital signs meet the inclusion-exclusion criteria for each study means that, at a minimum, healthy volunteers must maintain their weight, avoid taxing their bodies through exercise or stress, and try to be relaxed during blood pressure readings. Third, even if they match the protocol requirements, they must still be selected for the study. Participants might be invited to enroll based on who has the "best" lab values—such as measures of their blood levels or organ functioning—or on the order in which they screened or called in for their results. Finally, even if selected for a study, participation is not guaranteed. Clinics always overenroll healthy volunteers in each Phase I trial. If, for example, a study requires 12 participants, the clinic often brings in 16 with the expectation that it will dismiss four. The extra participants are referred to as "alternates," "backups," or "reserves." The clinics do this because they want to fill all their study spots for each group of healthy volunteers, and they have to ensure, first, that everyone who is selected to participate will actually check in on the day of the study and, second, that all those individuals will again pass all the required screening tests and remain eligible for the study. Healthy volunteers cannot rest easy that they are in the study until after they have "dosed" (i.e., taken the investigational drug or placebo). Together, these obstacles to participation mean that Phase I trials are a precarious source of income.

So-called professional participants try to improve their study chances through various tricks of the trade. They often develop relationships with recruiters and other research staff in the hopes that their good rapport will result in favoritism. Preferential treatment can manifest in terms of being selected for a specific trial or even being given information

about upcoming studies so they can know when to call for a screening appointment. Professionals also frequent numerous clinics to increase their opportunities for studies. Indeed, some travel extensively around the country and are thus able to expound upon the virtues or drawbacks of clinics in Austin (Texas), Baltimore (Maryland), Los Angeles (California), Madison (Wisconsin), Daytona (Florida), Neptune (New Jersey), New Haven (Connecticut), and so on.

By enrolling at multiple clinics, serial participants can also choose to disregard the stipulated washout period between studies and maximize the amount of money they earn from Phase I trials. The washout period is the window of time—usually no shorter than 30 days—during which participants are not allowed to join a new study. Established as part of study protocols both for the safety of healthy volunteers and for the validity of clinical trial data, washout periods are difficult to enforce because there is no centralized registry of trial participants. Clinics keep track of their own study participants, but beyond that, they rely primarily on an honor system in which they ask healthy volunteers about the timing of their last clinical trial.[8] Because of the high density of Phase I facilities in some regions of the United States, even individuals who do not travel far for studies can ignore the washout period by rotating their participation between two or more clinics and providing false information about their trial history (Edelblute and Fisher 2015).

By disregarding the washout period between studies, healthy volunteers can enroll in a greater number of studies, but they might also be increasing their risk of harm. To counterbalance this danger as well as to enhance their health more generally, serial participants alter their health behaviors. Many quit smoking, stop using recreational illicit drugs, and abstain from alcohol. They also increase their consumption of vitamins and minerals, and they drink copious amounts of water to flush the investigational drugs out of their bodies. Health is not just something healthy volunteers have, but a precarious state that is affected by their behaviors and actions leading up to when they screen for studies. In short, *health is a commodity that must be produced* if serial participants want to continue to qualify for clinical trials. As one participant asserted, "Your health is your wealth," when you want to enroll in Phase I trials. Thus, for serial participants, a lot of time, energy, and even money must be invested to succeed at earning an income this way.

Serial participants' orientation to Phase I trials coupled with the confinement structure of the studies contribute to a community of healthy volunteers. Serial participants tend to be generous with information and inform new participants about their experiences. They also share information within their networks by sending text message tips about available studies, warning others about AEs to expect, and swapping advice about preparing one's body for the next study. At the same time, however, they can jealously guard information about studies to minimize competition. The mode is generally to take care of themselves first—secure that coveted spot in a screening lineup—and then help out fellow participants when they can.

Solidarity among healthy volunteers can also be understood in terms of the stigma associated with participation. Rather than talking about their participation in Phase I trials with family, friends, co-workers, or acquaintances in their everyday lives, many healthy volunteers keep their involvement in research a secret. This means that the primary people with whom healthy volunteers talk about clinical trials are other participants. By doing so, they simultaneously deepen their networks and their identities as Phase I participants.

Whom Would You Tell about Your Phase I Experiences?

If you did consent to participate in a clinical trial, how would you make sense of that activity? How would you feel about having tested an investigational drug? What would determine if it was a one-time occurrence or the start of a long-term career? Would it become a shameful part of what you had to do in order to make ends meet financially? Or, would it instead be a story that you told at parties to shock or amuse your friends or colleagues?

Most of us will never enroll in a Phase I trial. While many of us could use some extra money and some of us might even want to contribute to the development of safe and effective pharmaceuticals, we probably will not sign up for such a study. Perhaps our lives will not accommodate checking into a residential research clinic for a lengthy period of time; our jobs and families might be obstacles to participating even if we wanted to enroll. Perhaps we fear that we will be injured or harmed, that the risks of the experimental drug cannot be justified. Perhaps we simply cannot qualify for a study—we may be too sick, too old, too fat, or too female.

Framework for Analyzing Phase I Clinical Trials

The fact that Phase I participation is rare among us means that it remains an unknown yet stigmatized world, with healthy volunteers often derided as being human "guinea pigs" or "lab rats." This book explores that hidden world by going into six Phase I research facilities in the United States—two on the East Coast, two in the Midwest, and two on the West Coast—to make visible healthy volunteers' experiences of adverse events within and outside the research clinic. Drawing upon my ethnographic work, I describe my observations of Phase I clinical trials, giving voice to healthy volunteers' and clinic staff's perceptions of the research enterprise.[9]

At the same time, to demystify Phase I research requires analyses of healthy volunteers' social context *and* the social construction of the science undergirding these clinical trials. On one hand, individuals' decisions to enroll in trials as healthy volunteers are predominantly motivated by adverse life events that often accrue for those at the bottom of the social and economic hierarchy. On the other hand, the Phase I industry's reliance on serial participants to generate data on drug adverse events undermines the validity and generalizability of these critical safety trials. This is because serial participants' focus on qualifying for studies makes them more and more suitable for the controlled nature of Phase I trials and less and less representative of the general population.

This book argues that US Phase I trials are fundamentally built upon and shaped by social inequalities and that the resulting system exploits participants to make pharmaceutical products appear safer than they really are. To explicate each part of this broader argument, I develop two concepts: *imbricated stigma* and *the healthy volunteer as a model organism*. These two organizing concepts anchor this book's discussion of Phase I trials in micro- and macro-level phenomena because both focus on the individuals who enroll in Phase I trials as well as on the broader political and economic context for their participation. Additionally, both engage the human-guinea-pig label in different ways. The concept of imbricated stigma acknowledges the multiple forms of stigma to which healthy volunteers are subjected, including but not limited to the stigma of research participation, whereas the concept of the healthy volunteer as a model organism, with its reference to nonhuman

animal research, elucidates how serial participation is a deliberate and indispensable part of Phase I science. This latter concept shifts the focus from healthy volunteers' personal motivations in order to query the norms of the profit-driven Phase I industry and the practices of research staff. While each concept performs important analytic work on its own, the book's argument can be rearticulated through their dual lenses: profound social inequalities manifesting in imbricated stigmas create the structure for healthy individuals to become human model organisms, restructuring their lives and behaviors in the service of the Phase I industry. While it may seem intuitive that Phase I trials' highly controlled environment bears little resemblance to real-world conditions, it is also the case that everyone involved—from the pharmaceutical companies sponsoring the studies, to the clinics conducting them and the healthy volunteers paid to participate—is incentivized to game the system in ways that ultimately generate validity concerns and may threaten public health. Developing these concepts below, I further define each of them and illustrate their value in analyzing healthy volunteers' participation in Phase I trials.

Locating and Theorizing Stigma in Phase I Participation

Medical research is deeply associated with images of guinea pigs and lab rats. These creatures are not only conjured to describe nonhuman animal research, but they are also used pejoratively to depict the role of human subjects in the research enterprise. The connotation of such terms is that participants are dehumanized by researchers: they are used like laboratory animals, cannot benefit, and will likely be harmed or even killed by the experiment. Moreover, there is often the implication that human subjects are being duped by researchers who do not tell them full and truthful information. Some may protest that this view of research does not share much in common with the majority of contemporary clinical trials, in which detailed (if not overwhelming) information is always provided about studies through the informed consent process and in which the possibility for therapeutic benefit is often present. Yet, the image of human lab animals still prevails and can be witnessed in the assertions of those who reject research participation by saying they do not want to be "guinea pigs."

The prevalence of this human-guinea-pig trope underscores the stigma associated with clinical trial participation. Medical research has long been associated with mad scientists, body snatchers, and other frightening scenarios (e.g., Kirby 2002; Lederer 1995; O'Neill 2006). The documented historical abuse of black participants in the US Public Health Service's infamous Tuskegee Syphilis Study fueled distrust of researchers, which has created a barrier to recruiting minority participants to therapeutic clinical trials and thereby denies these groups the prospect of gaining direct medical benefits (Corbie-Smith et al. 1999; Corbie-Smith, Thomas, and St. George 2002; Reverby 2000; Shavers-Hornaday et al. 1997).

While this stigma does not seem to prevent minorities from enrolling in Phase I trials, it nonetheless affects how healthy volunteers *experience* their participation, especially in how others perceive their involvement in research. This is all the truer for Phase I trials because healthy volunteers seek the financial reward of enrolling, not the potential for a cure for or the amelioration of a disease (motivations that have some credibility in explaining participation in later-phase clinical trials). Enrolling in research solely for money can signal to others that one's financial situation is dire—and dire enough to disregard one's health or personal welfare. Thus, within this frame, clinical trial participation as a healthy volunteer becomes a shameful act because only desperation would encourage someone to do it.

However, stigma surrounding Phase I participation is much more complex than what is suggested by its association with laboratory animals. Individual healthy volunteers are subject to multiple types of broader social stigmas that form the backdrop of their participation. In other words, healthy volunteers are typically already stigmatized in some capacity and face resulting forms of discrimination before they ever come to clinical trials. For some, it could be the stigma of being poor, being a racial minority, being an undocumented immigrant, and/or having been incarcerated. For others, it could be the stigma of being young, having limited education, being unemployed, and/or even being a political activist. These forms of stigma can be compounded, neutralized, or even mitigated by the stigma of being a research participant.

In his pivotal work on stigma, Erving Goffman (2009 [1963]) underscores that stigma is produced by social relationships in which some

individuals are cast as "normals" whereas others are seen as tainted or discounted, having a "spoiled identity." The power of stigma is that it is a form of discrimination that reduces some individuals' life chances based on essentially arbitrary factors that mark those individuals as less than normal. Discrimination, however, requires recognition of the stigmatized other. Goffman illustrates that there are two forms of stigma: discredited and discreditable. *Discredited stigma* is that which is visible and observable. It could include visible markers of race, such as the color of someone's skin, or disability, such as use of a wheelchair. In contrast, *discreditable stigma* is not readily observable and relies on the transmission of information about an individual's identity, behaviors, or other characteristics. Because of the material effects of being stigmatized, individuals can attempt to "pass" by concealing discreditable stigmas from others. Goffman gives the examples of mental illness and homosexuality as forms of discreditable stigma that can be hidden so that the individual can pass as normal in society. Phase I trial participation would be another form of discreditable stigma. The challenge for those with such stigmas is to manage information about themselves so that they will not be subject to discrimination or loss of personal relationships. In some instances, Goffman argues, individuals might choose to reveal a less stigmatized part of their identities to mask the "real" stigma and pass as nearly normal.

To understand the multiple forms of stigma that healthy volunteers encounter as part of their lives within and outside the Phase I clinic, I propose the concept noted earlier of *imbricated stigma*.[10] "Imbrication" typically refers to the overlapping pattern dictating how tiles or shingles are laid to create a surface that is stronger, more impenetrable, and more durable for its staggered structure.[11] Thus, I define "imbricated stigma" as the myriad combined stigmas that individuals face by virtue of how they look, the activities in which they engage, or the identities they inhabit. When imbricated, the component stigmas retain their own ignominy or social disadvantage for the individual, but taken together, they reveal the broader pattern of profound, tenacious inequalities through which material resources are distributed unevenly throughout society. Individuals are subject to different patterns of imbrication based on their social address and life experiences. Some individuals are subject to numerous stigmas, whereas others are relatively privileged, being white

or educated even if unemployed or poor. Thus, healthy volunteers as a group experience a range of stigmatized identities, with some of the component imbricated parts being more intractable and others more malleable.

Importantly, the effects of imbricated stigma are not solely repressive. While individuals themselves might face greater obstacles when fettered with multiple stigmas, they are not necessarily captive to these imposed stigmatized identities. Indeed, the more deeply imbricated the stigma, the more emboldened individuals might become to attempt creative solutions to combat their social disadvantage. This could include the decision to engage in another stigmatized activity, such as Phase I trial participation. For example, a young black man who is unemployed, never finished high school, and has a history of incarceration experiences imbricated stigma in the sense that each of these types of stigma can operate singly or in combination as he navigates his world. Like imbricated materials, the imbricated stigmas he experiences are obdurate, with race relations and economic opportunities highly resistant to change. In this context, the stigma of research participation can add one more form of judgment for him to face (perhaps from his family or friends), but a clinical trial can also relieve the stress of his other forms of stigma by providing an unparalleled economic opportunity that his history of incarceration, educational background, and skin color might routinely foreclose.[12]

Analyzing Phase I clinical trials through the lens of imbricated stigma helps to contextualize why individuals become involved in medical research and how, once enrolled, they perceive their study participation. Rather than seeing clinical trial participation as random and equally open to anyone in society, imbricated stigma focuses attention on the specific pattern of how and why certain segments of the US population are the most likely to enroll.[13] Groups with the most social disadvantages are the most likely to prioritize the benefits of participation over the risks. Participation rates bear this out, with minority men not only being overrepresented in Phase I trials more generally but also being more likely than non-Hispanic whites to become *long-term* serial participants. Specifically, of the 235 healthy volunteers in my sample, the six people who had participated in more than 50 clinical trials were black men, and more than a third of black healthy volunteers had

participated in more than ten studies (29 out of 84 participants), a rate twice that of whites (15 out of 88).[14] Hispanic healthy volunteers were also typically serial participants, but they generally did not have the same long-term pattern of study enrollment. Indeed, nearly two-thirds were in their third through tenth study (30 out of 50 participants), and only two Hispanic participants had enrolled in more than ten studies. In contrast, the whites in my sample were in the majority only when it came to being *first-time* healthy volunteers—a circumstance that suggests that perhaps with no racial source of stigma, they were more likely to participate in clinical trials as a single-time event rather than a recurring activity.[15]

Beyond the numbers, I illustrate throughout this book how these patterns of participation are inflected *qualitatively* by different imbrications of stigma. In particular, healthy volunteers variously adopt or reject the identity of a research participant (or professional lab rat) based on how they see themselves and feel perceived by others in nonresearch contexts. Additionally, immigration politics play out in how healthy volunteers perceive each other on the West Coast, with non-Hispanic participants accusing Spanish-speaking immigrants of stealing study opportunities from "Americans." Imbricated stigma also affects healthy volunteers' and research staff's perceptions of how individuals engage information about the risk of clinical trials and their decisions to enroll in studies. Imbricated stigma thus creates a basis for judgment about who is well informed about and well suited to Phase I trials.

Analyzing Healthy Volunteers as Model Organisms

Returning to the image of the human guinea pig or lab rat, the metaphor might be especially apt for healthy volunteer clinical trials compared to later-phase trials on affected patients. The typical confinement structure of Phase I trials can be seen as simulating the laboratory conditions used for nonhuman animal research. Once inside the clinic, participants are subjected to a controlled environment and the specific trial protocol. Notably, these conditions are quite artificial compared to the so-called real world in which people can exercise and consume whatever foods and beverages they desire. Frequent medical procedures, such as collection of blood, urine, feces, and even cerebrospinal fluid, are performed

to detect physiological responses to the investigational drugs because these might be so subtle that participants would be unaware of the changes to their bodies. Thus, healthy volunteers, just like actual lab rats, are housed in a clinic environment, must eat what they are given, are poked and prodded for data collection, and cannot benefit medically from the protocols.

The structural similarities between healthy volunteer clinical trials and nonhuman animal research motivate this book's second organizing concept: *the healthy volunteer as a model organism*. Within laboratory sciences, the term "model organism" refers to nonhuman animals that have primacy for researchers addressing certain questions across laboratory contexts. Model organisms are selected based on assumptions about which animal is the best suited to investigate scientific questions related to the etiology and natural histories of diseases or to provide preliminary evidence about the safety and efficacy of novel medical treatments.[16] Typically, the scientific value of nonhuman animal model organisms is based on how well these models extrapolate or "translate" to humans.[17] Likewise, Phase I trials use healthy volunteers as a model for the safety and tolerability of investigational drugs, and the data generated have value because of assumptions about the results' generalizability from healthy volunteers to diseased populations.

Model organisms are also selected based on nonscientific criteria, such as cost, efficiency, and ethics. For example, mice have become the dominant animal in research because they are relatively inexpensive, easy to breed or procure, and do not elicit as much moral controversy as do nonhuman primates.[18] Healthy volunteers serve a similar purpose in drug development. They are cheap, relatively easy to recruit, and raise few ethical concerns. Indeed, bioethicists and ethics review boards often prefer the use of healthy volunteers because such participants are less likely to have therapeutic misconceptions about their involvement in research compared to nonhealthy volunteers, particularly patients with terminal diseases, who are used in a much smaller number of Phase I trials.[19]

Models, by definition, are never perfect representations. They can nonetheless be made "good enough" through a process wherein scientists engage in calibration of the animal and disease models as they plan and make judgments about their experimental designs (Lewis

et al. 2012). Regardless of the limitations of model organisms, they remain critically important to biomedical science. One feature of the standardization they provide is that they operate as a type of currency that researchers can use to exchange scientific results.[20] By using the same model, researchers belong to a collaborative—and simultaneously competitive—community advancing a larger scientific agenda that can benefit from the discoveries of individual labs. In this way, the model organism is its own baseline onto which knowledge can accrue. As such, it is a known quantity; researchers know what to expect from it because of the extensive work previously conducted on it. Moreover, by relying on the predictability of a model organism, researchers can eliminate "rogue variables" from their research.

This leads to my definition of the healthy volunteer as a model organism: healthy volunteers are made into a specialized test subject through the act of their trial participation in order to produce particular types of scientific results. As with nonhuman animal research, attention to the social construction of the model productively highlights that science is an institution, with its own cultures and politics.[21] This framing nonetheless begs a question: What transforms an individual clinical trial participant into a model organism? One key piece is that healthy volunteers do not come to Phase I trials as they are; they need to modify their habits and prepare for each study. Doing so could be as simple as observing all the prescribed restrictions prior to checking into the clinic. These include relatively common things, such as 12-hour fasts; abstaining from caffeine, alcohol, vitamins, and supplements; and foregoing any moderate to high-intensity physical activity. It might also include specialized restrictions depending on the clinical trial, such as avoiding charred meats and cruciferous vegetables.[22] These requirements prior to a trial's commencement are designed to create a physiological baseline across all participants, simulating standardization through limitations on what healthy volunteers can and cannot do. In some instances, these are simply temporary changes to healthy volunteers' health behaviors, but for serial participants, as I noted above, restrictions are often incorporated into their broader lifestyles so that they are always ready for a clinical trial. In other words, being a healthy volunteer needs to be worked at: one needs to become the type of organism required for the science, not just be a generally healthy person.

Additionally, the seriality of their Phase I participation positions the majority of healthy volunteers as a type of model organism. Having a pool of participants who are willing and able to adapt to the structure of Phase I trials is a critical element of the science. Healthy volunteers who enroll repeatedly in clinical trials might differ from the general population in their ability to tolerate investigational drugs or, more practically, the confinement period (Sibille et al. 1998). Serial healthy volunteers are self-selecting based on their prior experiences in trials, which are typically positive, otherwise they might choose not to enroll in subsequent trials. Just as laboratory-based researchers rely on a constant supply of nonhuman animals to continue their work, the Phase I industry as a whole depends on serial participants to fill the thousands of Phase I studies conducted each year. Without individuals who continue to enroll—regardless of how often each person actually participates—recruiting healthy volunteers would likely take much longer and trials would be more difficult to conduct.

Another way in which healthy volunteers become model organisms is a result of Phase I clinics' selection of individuals who have done prior studies with them. While I have referred to healthy volunteers with a history of enrolling in Phase I trials as "serial" participants, this moniker does not make distinctions based on which clinics those participants frequent. Whether someone participates solely at one clinic or travels to clinics all over the country, it is the regularity of their enrollment in trials that makes them serial participants. In contrast, the clinics describe healthy volunteers who have already completed studies with them as "repeat" participants. Research staff have strong preferences to enroll repeat participants because those healthy volunteers have already been vetted.[23] Repeat participants typically have a lower screen failure rate than the general public, are accustomed to the clinic and its rules, and are expected to complete the studies. In this way, repeat participants are known quantities from the point of view of the research staff, whereas prospective healthy volunteers with whom the staff have no direct personal experience are rogue variables and raise the question of how well suited to Phase I trials they might be. This privileging of repeat participants affirms their status as model organisms because clinics' supply of healthy volunteers is actively curated and relatively circumscribed.

An important benefit of analyzing the healthy volunteer as a type of model organism is that it places individuals' decisions about their participation in Phase I trials within the larger system of science. There has been much attention within the field of bioethics to the "subversive" character of serial participants,[24] but there is also a perverse tendency to blame the individuals who engage in deceptive practices, such as ignoring the washout period between studies. This position fails to question how the Phase I industry itself enables, and at times encourages, some serial participants' rule-breaking. I train my focus instead on how the research enterprise creates incentives and disincentives that structure the practices of everyone involved. The model organism framework places emphasis on the practices both of healthy volunteers *and* research staff.

Book Overview

By placing these two concepts—imbricated stigma and the healthy volunteer as a model organism—at the center of my analysis, my goal is to underscore both the social inequalities on which the research enterprise is built and the agency of individuals as they navigate their study participation within the structure of Phase I science. This is not a story about Big Bad Pharma, although it could be.[25] It is about how experiences of being a healthy volunteer are embedded in a larger social context, which is often characterized by discrimination and economic insecurity. The scientific context is also important because it necessitates that healthy volunteers submit to the controlled conditions dictated by the study protocols, and it rewards those who are best suited to the environment by selecting them for additional trials. While Phase I trials are not necessarily transformative experiences for healthy volunteers, participation in these studies can nonetheless disrupt traditional responses to stigmatizing conditions by offering a new, but potentially risky, mechanism to get ahead. Of course, Phase I trials do not guarantee healthy volunteers' success in reshaping their lives, but they do create an alternative economic pathway that, as the following chapters illustrate, includes not only risks but also important nonfinancial rewards.

To begin our journey into the world of Phase I research, chapter 1 provides ethnographic detail about entering and being confined to a clinic. It aims to create a sense of place by examining what one such

clinic looks like and how it operates as well as the clinic's social world, including the camaraderie and conflicts among healthy volunteers. I also describe my methods, including how I gained access to the clinics, how much time I spent conducting this research, and demographic information about the research staff and healthy volunteers I interviewed.

Chapter 2 turns our attention to the economic motivations of healthy volunteers. Drawing upon the concept of imbricated stigma, I describe how individuals' social positions shape their view of Phase I trials. I examine not only the catalysts in their lives that lead to study enrollment but also how economic need, employment opportunities, and consumer culture influence how participants view the value of study compensation. There are, however, differences in the cultures of Phase I participation based on the region of the country. Chapter 3 focuses on this theme to further unpack variations in how patterns of imbricated stigma influence healthy volunteers' perceptions of Phase I trials, particularly with respect to the longevity of their study involvement.

Chapter 4 examines the Phase I clinics. I provide a brief history of the Phase I industry to contextualize the opportunistic nature of many of the clinics that are currently operating in the United States. Clinics' concerns about profitability and/or reputation lead to different investments in their facilities and staffing, which in turn result in a wide variation in experiences for healthy volunteers depending on where they enroll.

Turning attention to study protocols in chapter 5, I describe the highly controlled nature of Phase I trials and how research staff actively cultivate healthy volunteers as model organisms by conditioning them to the demands of the trials. These practices by research staff also raise important validity concerns about Phase I trials, which are analyzed in chapter 6, focusing particularly on how healthy volunteers, clinics, and the pharmaceutical industry are all incentivized to make investigational drugs appear safe.

A book on clinical trials would be incomplete without a discussion of risks. In chapter 7, I draw on secondary data about the safety of Phase I trials to discuss how research staff and healthy volunteers alike struggle to make sense of the omnipresent hypothetical risks of studies outlined in consent forms in the face of tangible evidence of the trials' relative safety. Healthy volunteers' construction of trials as safe is further enabled by their categorization of some studies as riskier than others. In

chapter 8, I describe these risk constructions as a type of model organism epistemology, illustrating how this knowledge comes from personal experiences as well as stories and rumors they hear from other participants. Regardless of the veracity of their claims about risk, healthy volunteers mobilize this information about Phase I trials when deciding which studies to join and which to avoid.

Next, chapter 9 takes a different tack on the discussion of risk. While healthy volunteers are concerned about Phase I trial risks, they are often much more vocal about the economic risk of *not qualifying* for studies. This chapter examines how being disqualified from studies heightens their sense of risk as they attempt to earn income through clinical trials, which profoundly influences their health behaviors even outside of their study participation. These actions on the part of healthy volunteers indicate that Phase I participation could improve their general health even as they expose themselves to the unknown risks of investigational drugs.

Finally, the book's conclusion reflects on the political and economic context of US Phase I trials. A society characterized by deeply imbricated stigmas ensures that there will always be healthy volunteers willing to enroll in Phase I trials, whether these are the same or new participants who need the financial compensation. Ultimately, attending to the underlying social inequalities animating the Phase I industry is critical to understanding what is at stake when healthy volunteers are used in drug development.