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The Gravity of Weight

Guinea Pigging: Healthy Volunteers in Phase I Trials

"Captives of circumstance" may participate in clinical research.

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Bottle of quinine hydrochloride tablets,used to treat malaria, from Burroughs Wellcome and Company, Limited, 1901-1930. Science Museum of London. Burroughs Wellcome and Company, led by Henry Wellcome from the late 19th century, was one of the first pharmaceutical companies "to place research on a scientific footing," according to the Science Museum.
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"Wanted: Patients for Vaccine Trials" reads the boldface headline on page one of the *Wall Street Journal*. “Given the urgency” of the rampant spread of COVID-19, researchers are making an “unprecedented effort to recruit thousands of healthy volunteers,” and trials are “effectively competing with each other” for their subjects (*WSJ*, Hopkins and Loftus, pp. A1, 6, 7/6/20). Studies with thousands of volunteers are Phase III trials, i.e. late-stage trials done to assess safety and efficacy of a medication or a vaccine. Earlier testing, though, begins with just a few subjects. These initial participants are the healthy human *guinea pigs* who volunteer for Phase I studies, often exposing themselves to potential risks in what are called “first-in-human” trials.

No one knows how the guinea pig got its name since it is neither pig nor from Guinea, but rather a rodent from South America (*Oxford English Dictionary, OED*). Reportedly, though, docile guinea pigs have been used in scientific research since the 17th century and continue to be used today, though they have mostly been replaced in recent years by rats and mice. George Bernard Shaw, Upton Sinclair, and H.G. Wells were among the first, in the early 20th century, to use *guinea pig* to refer to a person who is the subject of an experiment (*OED,* “guinea pig”).

"Guinea pigs," 1792, painting by George Morland. Guinea pigs have been used in research since the 17th century, but the term "guinea pig," to indicate a person subjected to scientific research, first appeared in the early 20th century and used by writers such as H.G. Wells and G.B. Shaw.
Source: Bridgeman Images, used with permission. Credit: The McManus Dundee, UK Dundee Art Galleries and Museums.

Up until the 1970s, an estimated 90 percent of drug trials were conducted on prisoners, but this practice was banned a year after the publication of the Belmont Report (1979) that emphasized the importance of consent in human research (Abadie, *The Professional Guinea Pig: Big Pharma and the Risky World of Human Subjects*, 2010).

The world of Phase I drug trials is “largely invisible,” and unknown to most of us, writes Jill A. Fisher in her new book, *Adverse Events: Race, Inequality, and the Testing of New Pharmaceuticals* (2020). Fisher, for her study of Phase I trials, interviewed, both formally and informally, 235 participants and staff from clinics supported by different agencies, including the pharmaceutical industry, an academic medical center, for-profit local research clinics, and CROs—contract research organizations. In her sample, most were ethnic and racial minorities: 35 percent African Americans, 22 percent Hispanic, 4 percent Asians, and 1 percent Native Americans.

Fisher found differences in both the quality of the facilities and their staff. The for-profit clinics, in particular, cut corners by providing broken furniture, no amenities to alleviate the boredom, and poor quality of the food. More importantly, some hired untrained and even unprofessional staff who were not even adept at phlebotomy. This

"Bath for Prisoners in Portoferraio," (Elba Island) by Italian artist Telemaco Signorini, circa 1890. Before the 1970s, about 90% of all drug testing was conducted on prisoners, a captive and compliant population. This practice stopped after the publication of the Belmont Report that emphasized the importance of consent in human research.
Source: Wikimedia Commons/Public Domain.

is particularly unfortunate since these Phase I trials are often called the “feed ‘em and bleed em’" studies (Fisher, 2020).

What Fisher found is that clinical trial participation among these healthy (and mostly young to middle-age) volunteers is highly stigmatized. Most often, their involvement reflects their desperate financial situation about which they feel embarrassed. This type of research “unfairly targets” lower socioeconomic, mostly minority populations, who are often unemployed with limited job possibilities due to bad credit, debt, illegal alien status, or even a history of incarceration. She found that most participate repeatedly: six in her sample had been in more than 50 trials. Some investigators had met those who had participated in 70 to 80 such trials! (Abadie, 2010).

"The Phlebotomist Taking Blood," by Mary Rouncefield. Phase I clinical trials have been referred to as 'feed 'em and bleed em' studies. Some clinics, for cost-cutting, will hire staff poorly trained and inept at drawing blood.
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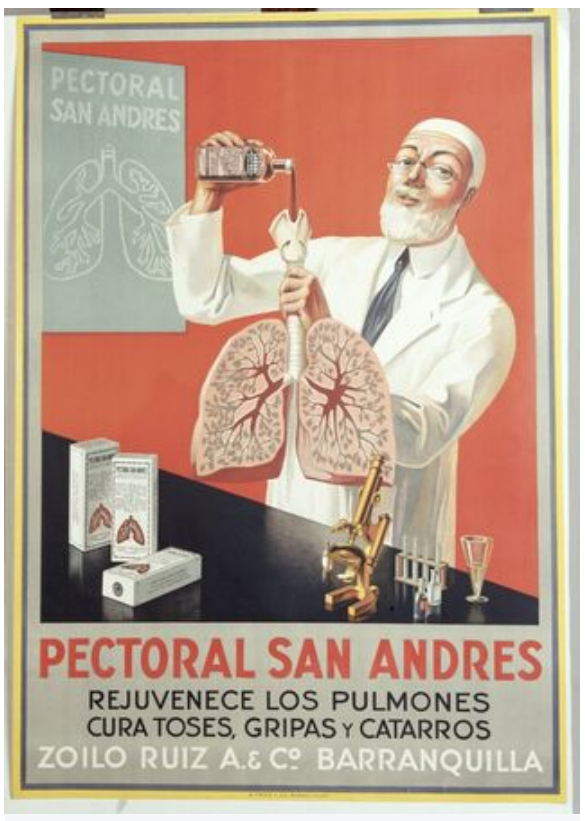
Compensation, used both to recruit and retain, with the promise of a “completion” bonus, is the “primary, if not sole motivator” for these volunteers. In her paper with colleagues (Walker et al, *Journal of Medicine and Philosophy*, 2018), Fisher writes of *structural coercion,* i.e., the ways in which broader issues of social, economic, and political disparities "compel" these people to volunteer. These healthy participants are *captives of circumstance* (Hans Jonas, *Daedalus,* Spring, 1969). The “adverse *study* events just pale in comparison to the often-incessant adverse *life* events" that these people experience, writes Fisher (2020).



A pharmaceutical chemist demonstrating the effect of Pectoral San Andres on the lungs, circa 1925.
Source: Wellcome Trust Collection/Public Domain. Zoilo Ruiz A & Co, Colombia. Attribution 4.0 International (CC by 4.0)

Paying people to test for drugs they don't need and in all likelihood, would never be able to afford, is a way of "commodifying the body" (Abadie, 2010). It is Abadie who coined the term *guinea pigging* to refer to these healthy serial participants who are paid to "endure" (2010). Some ethicists experience these trials as "exploitative" since there is *no therapeutic intent* (Johnson et al, *Clinical Trials*, 2016; Wikler, *Journal of Medical Ethics*, 2017), and the trials become a "commercial relationship" (Dickert and Grady, *New England Journal of Medicine,* 1999).

Phase I studies include studies that test a drug (some are already FDA approved in one form, while many are not) in single or multiple doses; compare different formulations of a specific drug, measure interaction with other drugs, and assess how a food can affect a drug. These trials also are concerned with how a drug is absorbed, metabolized, and excreted, as well as how the drug acts on the body (Fisher, 2020). They target healthy volunteers because these subjects don't have confounding illnesses that might affect a drug and are not on any other medications that might complicate the results. This population, though, is often not representative of the general population.

Essentially, Phase I trials, says Fisher, "tackle how much of a drug can be given to healthy subjects without inflicting too much harm" (Fisher, 2020). There is no Phase I clinical trial, though, without risk, which can be considered in terms of time (e.g. short-term vs. long-term) and severity (Abadie, 2010). Fisher notes that researchers refer to adverse *events* rather than adverse *effects.* Often subjects themselves judge risk by their own experiences, particularly over multiple trials, as well as by discussion with other Phase I participants

(Abadie, 2010). Because of compensation that can be quite substantial (e.g. many thousands of dollars for each study), subjects have an incentive to give false information (including deliberately failing to mention adverse events) or even failing to adhere to required wash-out periods between studies. Further, they construct "counter-narratives" that tend to minimize these events. For many, because of the financial compensation, the greatest risk is *not* qualifying for a study or being asked to leave a study because of reactions to the study medication. (Fisher, 2020). A survey of healthy subjects found more than 1/3 did not know whether the medication they were receiving was FDA-approved; some did not know there would be 40 blood draws during the 17 days or how many outpatient visits were required. Significantly, though, *all* 30 of the subjects knew exactly how much money they would be receiving upon completion (Apseloff et al, *American Journal of Therapeutics,* 2013).

In general, though, Phase I studies involve mild and moderate risk. In one review of 475 trials and over 27,000 healthy participants, there were no serious events related to the studies (Johnson et al, 2016). There have been, however, a few disastrous studies--one involving the"darkest day" in the history of clinical trials (see Mishra et al, *European Journal of Clinical Pharmacology*, 2020 for the BIA10-2474 study that led to brain necrosis and hemorrhage in all healthy participants) and another involving the infamous TGN1412 in which all six subjects required ICU care and had lasting effects. (Stebbings et al, *Current Opinion in Biotechnology*, 2009; Eddleston et al, *British Journal of Clinical Pharmacology*, 2016).

"An Alchemist in his Laboratory," painting by a follower of David Teniers the Younger. Drug development has changed significantly since the alchemists of the 17th and 18th centuries.
Source: Wellcome Trust Collection/ Attribution 4.0 International (CC by 4.0)

Pharmacy jar, Spanish, 1420-1430.
Source: Metropolitan Museum of Art, NYC/Public Domain. Credit line: The Cloisters Collection, 1956

With the TGN1412 study, researchers had miscalculated the dose given because macaque monkeys, used as the animal model, had no reaction to the antibody. Here is an example of the oft-quoted phrase, "Absence of evidence is not evidence of absence" (Stebbings et al, 2009). Choosing an appropriate animal model for pre-clinical trials, i.e., conducted prior to "first-in-human" studies, though, is often difficult. There is always a "level of uncertainty" when researchers translate human doses from animal models and hence "make subjects vulnerable to harm" (Dresser, *The Journal of Law, Medicine & Ethics*, 2009). There are several ways of determining a human dose, based on *NOAEL*--"no observed adverse effects level," the most frequently used calculation. More recently researchers, partly as a result of the TGN1412 disaster, are using MABEL--"minimal anticipated biological effect level" as a safer alternative (Suh et al, *Drug Design, Development and Therapy*, 2016; Mishra et al, 2020).

With continued dire predictions about the COVID-19 pandemic, investigators are rushing to produce an effective vaccine and effective treatments. "Pressurized research" during times of emergency, though, can lead to "false promises, disastrous consequences, and breaches of ethics" (Doroshow et al, *Annals of Internal Medicine*, 2020). Ironically, many healthy volunteers refuse to enter vaccine studies as they view them as too dangerous (Fisher, 2020; Johnson et al, 2016).

Bottom line: Healthy people, often minorities and the severely disadvantaged, may volunteer repeatedly for Phase I trials because they are *captives of circumstance*, i.e., desperate due to life events (and particularly their financial situation) that they may perceive as far worse than any risks they may encounter in clinical trials. Relying on these serial participants, who subject themselves to countless trials, though, may compromise the validity and generalizability of Phase I studies since these subjects are hardly representative of the general population. Further, to what extent these volunteers subject themselves to greater synergistic dangers by their serial participation is not known. Financial incentives often encourage them to minimize risks and even fail to

report negative effects from the medications for fear of being asked to withdraw from the study and lose their compensation. Many researchers have suggested the creation of a centralized database to monitor and protect these people, often from themselves.

About the Author

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