Professional Volunteers: Human Guinea Pigs in Today's Clinical Research

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ABSTRACT

Pharmaceutical researchers are not only concerned about finding the most appropriate population of volunteers, they also need to do so as quickly as possible. The long-standing adage "time is money" is noticeably at play here. The more time the company takes to complete the enrollment of a sufficient number of subjects, the more time is taken away from the actual progression of the clinical trial. In order to achieve the best possible results in Phase I, the drug's developer relies on healthy volunteers, for it is a healthy population that is, "an indispensable requirement of the experimental design employed in the randomized clinical trials." A healthy population helps to ensure that all participants start the trial in the same medical condition.

Keywords: research ethics, volunteers, research subjects, international medical research

INTRODUCTION

In 1939, Dr. William Osler Abbott used his opportunity with an audience at the Charaka Club in New York to recount the process for conducting necessary clinical research for his new gastroenterological technique for treating obstructions in the small intestine. The Miller-Abbott tube, as it is known, is a 10-foot long, double-lumen tube with a rubber balloon at the end which is blown up inside the intestine. After its development, Abbott was immediately advised to test the new device in animals. However, he found this exercise to be a "waste of time" and instead focused his efforts on the "capture, selection, care and training of good healthy human guinea pigs".[1] In doing so, Abbott went against the better judgment of his colleagues, but he was also adhering to the tradition of experimental medicine set forth by Claude Bernard in the mid-19thcentury: "it is our duty and our right to perform an experiment on man whenever it can save his life, cure him or gain him some personal benefit".[2] Regardless of his determination, Abbott's contemporaries were skeptical of his ability to find healthy men and women eager to subject themselves to intubation, and rightly so. Abbott's research team made itself unpopular in the various hospital wards trying to find suitable

patients, and despite it being the height of the Great Depression, agencies, churches, and welfare organizations could not provide anyone keen on taking the $2 job as a human subject. Even the destitute and desperate in Philadelphia were unwilling to follow the doctor for a "short day's work" at the hospital.[3]

ANALYSIS

It was not until Abbott utilized a black janitor's useful skill as a broker that willing research subjects began walking through his doors. Within a short amount of time, the doctor was able to keep his "animals" in firm control. Yet in 1935, Abbott quickly learned an important lesson: human experimental subjects "are apt to be human". His research subjects grew wiser and went on strike, demanding a raise right before an important exhibition at the American Medical Association; thus doing what no "dogs, cats, rats or rabbits that [he] had ever handled had done."[4] Abbott was only able to escape this minor crisis by imploring and securing the help of third-year medical students at the University of Pennsylvania, offering them the same wage as his black professionals. Needless to say, Abbott's once-reliable guinea pigs were fired, and he was forced to find a fresh source of willing subjects. He soon realized that the most effective way to find someone to work for him was to advertise to the masses in newspapers, and it was not long before his office was inundated with dozens of male and female volunteers ready to accept the task. Abbott's problems were solved, and as he states in his closing remarks to the Charaka Club, "the honorable and rapidly growing guild of tube swallowers [was] well established."[5]

It has been almost three-quarters of a century since those proceedings at the Charaka Club, but this anecdote serves as a backdrop to show how this specific characteristic of clinical research has not changed much in that time. It has merely been updated to fit the needs of modern-day Dr. Abbotts who take the form of pharmaceutical and research companies. Phase I clinical trials have replaced Abbott's gastroenterological experiments, and they have exacerbated the phenomenon known as "guinea-pigging," in which seemingly healthy volunteers offer themselves up as professional research subjects in exchange for monetary compensation.

Phase I clinical trials are a vital step in a drug's progress from development to market. They are designed to test the safety of the drug, representing the first time that it is being exposed to human beings after having been evaluated in the laboratory and in animal subjects. Whereas Phase II trials are used to measure the appropriate dosing requirements and "demonstrate therapeutic efficacy" and Phase III trials are larger scale comparisons of the drug's efficacy against standard treatment, the purpose of Phase I is to ascertain the possible side effects of the drug treatment.[6] In order to achieve the best possible results in Phase I, the drug's developer relies on healthy volunteers, for it is a healthy population that is, "an indispensable requirement of the experimental design employed in the randomized clinical trials."[7] A healthy population helps to ensure that all participants start the trial in the same medical condition. Should any physiological or psychological changes arise during the course of the trial, researchers are able to attribute these outcomes to, "the drug regimens to which the volunteers were exposed."[8] To attain this kind of homogeneous population, clinical researchers screen potential candidates for existing medical conditions, making sure

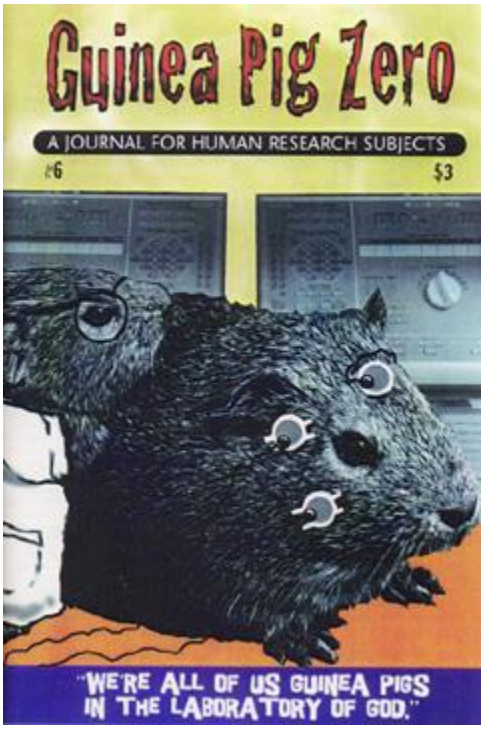
to minimize the risk to volunteers by eliminating potential drug interactions. The ideal participants must be drug-free, non-smokers, who do not take any medications, and do not have any congenital conditions.[9]

Pharmaceutical researchers are not only concerned about finding the most appropriate population of volunteers, they also need to do so as quickly as possible. The long-standing adage "time is money" is noticeably at play here. The more time the company takes to complete the enrollment of a sufficient number of subjects, the more time is taken away from the actual progression of the clinical trial. This causes delays in subsequent phases, the drug's FDA approval, and its introduction to the lucrative pharmaceutical market. Put one way, when a researcher was asked by the Office of the Inspector General of the Department of Health and Human Services about what sponsors were looking for when it comes to clinical trials, the researcher replied, "No. 1 – rapid enrollment; No. 2 – rapid enrollment; No. 3 – rapid enrollment."[10] Although speed is paramount, researchers cannot afford to rapidly enroll volunteers that do not meet the strict medical requirements, which would jeopardize the validity of the trial and put volunteers' health at risk.

The need to meet this overwhelming demand and expedite the process has caused a recent shift in the way Phase I trials are conducted. Whereas some pharmaceutical companies still prefer to run their own drug trials, many have found utility in outsourcing operations to universities and independent contractors known as contract research organizations (CROs).[11] CROs and other research institutions are incentivized to quickly attract a broad base of qualified research volunteers, for their recruitment and retention statistics are what make them stand out in the eyes of pharmaceutical companies. Therefore, they not only offer competitive compensation – which can range from several hundred to several thousand dollars depending on the length of the trial – but some of the more lavish trial sites offer individual suites, internet access, pool tables, flat-screen televisions, and other desirable amenities.[12] Although these facilities and financial benefits are a welcome improvement to the "prisonlike environments offered ten or more years ago", this market-driven approach has effectively created a "new dynamic" in clinical research.[13],[14] Essentially, the relationship between the researcher and the human subject has been relegated to that of a factory owner and a wage laborer. As Carl Elliott states, "the relationship…has become, more nakedly than ever, a business transaction."[15]

Much like Abbott's "guild of tube swallowers," there are those that seek to take advantage of the pharmaceutical industry's never-ending need for healthy volunteers and reap the financial rewards. These individuals make up what has become a, "sub-population of normal volunteers…who participate in several studies, either simultaneously or over time."[16] Whereas clinical trial participants in the later phases are usually sick and might be motivated by altruism or the hope at receiving the therapeutic benefits of the tested drug, these professional guinea pigs cannot expect, "any therapeutic benefit to balance the risks they take."[17] Moreover, they do not hide behind the fact that money was the main incentive that attracted them to the clinical trial. A survey aimed at evaluating the, "weight of financial reward and other general details as seen by healthy volunteers who had already participated in clinical trials," showed that 90% of "experienced volunteers" admitted that financial reward was the main reason to participate.[18]Additionally, the survey revealed that 83.7% of respondents felt the compensation was adequate compensation considering the time spent and discomfort during the trial.

In light of these admissions, someone unaware of this growing trend in subculture might ask: Who are these guinea pigs? Are they not aware that they are responsible for the commodification of their bodies? Roberto Abadie's ethnographic study of those who identify themselves as professional guinea pigs helps to answer these questions, providing insight into their lives. Abadie's study focused on 18 research subjects in Philadelphia, which, along with Houston, is considered a hotbed of clinical trials, offering plenty of "opportunities for aspiring human subjects."[19] Their ages ranged from 21 to 46, though most volunteers hovered around the mid- to late twenties. All but four of the volunteers were men; and all but one of them self-identified themselves as white or Caucasian. The volunteers also covered a broad educational spectrum: one did not finish high school, four graduated high school, six completed some undergraduate study, six completed their undergraduate studies, and one was enrolled in a doctoral program. While three of the volunteers were homeowners, the rest lived in communal houses while paying rent. Most did not have health insurance, with the exceptions of three volunteers who had employer-based HMO coverage. As was expected, when Abadie asked about volunteers' motives for entering clinical trials, all of the surveyed subjects declared that the trials were the ideal opportunity to "make easy money," "quick money," "a considerable amount of money in a relatively short time," and a "huge sum."[20]



Each of the professional guinea pigs studied by Abadie understood their bodies to be commodities within the clinical trial context. They readily accepted the fact that pharmaceutical companies compensate them as "short-term

contractors," for the "rent-use of the body and the inside operating fluids."[21] They understood that their role as trial subjects comprises a kind of work inherently different from physical labor. One guinea pig described it as such: "it's a weird kind of work in a 'mild torture economy' in which I am paid not to produce something, but to endure something."[22] For this guinea pig, success in his line of work depended entirely on his ability to tolerate whatever physical or psychological pain came with the trial.

This recognition on the part of such volunteers does a great deal to highlight the view held by industry--total denial that commodification takes place. Using a series of "rhetorical moves" – much like the ones employed by the egg donation and IVF industry –pharmaceutical companies use the term "paid volunteers," defined as those who, "receive financial compensation for time and travel expenses" to describe the guinea pigs.[23] This kind of language puts great stress and emphasis on the fact that the research subjects voluntarily enroll in the trials, which relieves pharmaceutical companies of any responsibility for the risks involved. However, this attitude disregards the reality that if not for the financial compensation, many, if not all, professional guinea pigs may not participate. They would, perhaps, seek out other ways to make "a quick buck."

Between 1990 and 2001 there was a threefold increase in the number of enrolled research subjects.[24] By combining this fact with the awareness that Abadie's study only takes into account a small number of the self-identified professional guinea pigs, one can speculate that the prevalence of professional research subjects will continue to rise as the number of industry and government-funded clinical trials increase. Such growth presents several ethical concerns that must be addressed for the sake of participant safety and the role of clinical research in medicine.

In the case of clinical studies involving pharmaceutical drugs, subjects who participate in trials simultaneously or in quick succession endure increased safety and health risks. This is because, "multiplying the number of investigational drugs absorbed by a subject over a relatively short period of time can considerably increase the risk of severe adverse drug reaction."[25] As mentioned above, financial compensation seems provide the greatest motivation for professional clinical trial participants. Many willingly sign on to concurrent or successive studies because of increased financial benefit. Such individuals may be ignorant of the risks inherent in that decision or choose to ignore the compounded risk altogether. A survey conducted in Germany concluded that almost half of repeat volunteers who admitted to providing deceptive medical information to researchers, "did not see any risk associated with providing unreliable information."[26] While study subjects may not see any risks in concealing the truth, the responsibility still lies with clinical researchers who must obtain appropriate information so to accurately discern candidate suitability for trials.

The fact that financial motivation incentivizes deceit about medical histories, raises key ethical questions about informed consent and undue influence. The preeminent and guiding document with regard to ethical conduct in human subject research, the Belmont Report, clearly shows the incompatibility of the practice of guinea-pigging with clinical trials. The principle of respect for persons maintains that research subjects must be able to act autonomously, "capable

of deliberation about personal goals and acting under the direction of such deliberation."[27] It is this principle that governs the process of informed consent, in which a capable research subject is free to choose what should happen to them. It could be argued that the professional subjects are not given all the necessary information to make an informed judgment regarding their willful participation in the clinical trial. Those who choose to deceive research investigators may be doing so without the knowledge that participating in numerous drug trials carries significant health risks, and it is the duty of the researcher to ensure that the information is imparted to and comprehended by the subject.

In addition, the subject's consent to partake in the research study is only valid if, "voluntarily given…and free of…undue influence," in which undue influence is constituted by offers of, "excessive, unwarranted, inappropriate or improper reward…in order to gain compliance."[28] In Abadie's study, professional guinea pigs were well aware of the substantial risks involved – many having experienced them first-hand – but continued to enroll in multiple studies, spurred on by the promise of a big check at the end of the trial. Many ethicists would argue that this alone suffices as undue influence--financial incentives hamper the ability to accurately weigh the risks and benefits associated with studies. Thus, stricter safety guidelines must be enacted and enforced for the subjects' safety. Others would say that restricting their ability to freely choose participation in light of the information equals paternalism, violating the subjects' rights to self-determination. Finding a balance between protection and paternalism without compromising the subjects' freedom of choice is a necessity moving forward. Finally, it is evident that the principle of justice is at play in this case. The Belmont Report stipulates that the burdens and benefits of research must be justly distributed among members of society. It seems clear that those who offer themselves up as guinea pigs, "because of economic necessity may unduly bear the burden," of clinical trials.[29] Because many subjects are uninsured and poor, they participate in testing the safety of drugs that they could likely not afford once approved and released. Guinea pig dependency on "contracts" with CROs and pharmaceutical companies makes them easy, convenient targets for recruitment. And, although some professional guinea pigs welcome the extra opportunities, this should not be the case for all volunteer research subjects.

Given the current influence that pharmaceutical and research companies have on professional guinea pigs, one possible solution might be to eliminate payments to human research subjects. Research could rely instead on altruistic reasons for participation. Without undue influence preventing truly informed consent and enticing professional guinea pigs, the problem would be solved and the risks associated with repeat volunteering averted. However, this is a very idealistic approach. If clinical trial sponsors relied solely on altruism, "studies on healthy subjects would probably come to a halt."[30] What drives the recruitment and retention of human subjects, especially guinea pigs, is the financial incentive. Removing that from the equation would remove an integral component of the current infrastructure of Phase I clinical trials. Christine Grady argues that denying research subjects money, "might have negative consequences because it could deny them a potential alternative income." It is evident some professional guinea pigs depend on the earnings from trials to live a, "marginal lifestyle."[31],[32]Sheldon Zink offers another rebuttal to the idea that halting payment would solve the issue. He points out that the, "healthcare system in the United States is a business based on payment for service and contracted agreements." Eliminating the opportunity for payment would potentially create a system of "real coercion for participation," marked by drug manufacturers going to great lengths to ensure enrollment of human subjects in studies offering no individual benefit.[33]

The arguments above demonstrate that a focus on the payment of professional research subjects may be misguided, and misses the heart of the issue: existing guidelines are ill-equipped to deal with professional guinea pigs. The current regulatory framework has not been able to keep up with the "exponential growth in academic and commercial research activity," and as a result, it has not been able to adequately address the rise of guinea-pigging.[34] The NIH strongly advises volunteers to be honest and forthcoming with medical information, instructing them to "let the investigator know your participation in any other research studies – past, present, or planned." Yet it fails to identify the maximum number of trials in which a volunteer may participate per year.[35] Furthermore, the FDA's guidelines for investigators state that, "trial subjects should not participate concurrently in more than one clinical trial…and should not be enrolled repetitively in clinical trials without time off treatment adequate to protect safety and exclude carryover effects."[36] However, these guidelines do not provide specifics as to what is considered "adequate time of" or the "carryover effects." By not providing enough elaboration and explanation to study investigators, the FDA is putting the onus on researchers to judge what is appropriate. Until federal guidelines are more straightforward in addressing the issue at hand, the current situation of professional guinea-pigging in clinical research will continue unimpeded.

Whereas the issue of "professional volunteerism" has received little attention in the United States, the United Kingdom and France have enacted restrictions and established centralized registries to keep track of the increasing number of volunteer human subjects.[37] Taking a similar approach, it seems only logical that responsible investigators maintain a database of volunteers at the institutional level. With these registries in place, investigators would be able to better communicate with each other regarding the participation of professional guinea pigs; and more importantly, they could "help prevent adverse events associated with a volunteer who is participating in simultaneous studies, or who has not allowed enough time to elapse between studies."[38] Analysis of the effectiveness of these institutional registries could provide insight into the proper implementation of a national registry of human subjects. These efforts are not meant to eliminate the freedom that guinea pigs enjoy in participating in clinical trials for the purpose of financial gain. They would, however, provide professional subjects with greater protections from unnecessary, increased risk.

CONCLUSION

The future of clinical research and the safety of new drugs will continue to depend on the willingness of healthy volunteers to participate in clinical trials. It seems "inevitable that the job will fall to people who have no better options."[39] Without much official guidance or protection, professional guinea pigs have to rely on each other and watchdog or independent groups, such as Citizens for Responsible Care and Research (CIRCARE) and CenterWatch, for reliable information regarding clinical trials and human subjects protection. Further investigation into the unique social and economic needs of this sub-population of human research subjects, like the ethnographic study undertaken by Roberto Abadie, is an essential step in the construction of an ethical and practical framework aimed at improving the conditions of clinical research and ensuring the safety of trial participants.

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