Healthy Volunteers

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Abstract and Keywords

This chapter describes the involvement of healthy volunteers in biomedical research. Healthy individuals are valuable to research because they can offer data about biological processes or investigational products that are not distorted by illness or disease. In addition, healthy individuals are generally much easier to recruit to research than are ill patients. Recruitment of healthy participants is aided by the offer of financial compensation in exchange for their participation. The involvement of healthy individuals in research is meant to resolve ethical problems associated with enrolling patients, such as exposing sick individuals to risk and creating misunderstandings for patients about the difference between research and clinical care. However, as this chapter details, using healthy individuals in biomedical research raises different concerns about risk exposure as well as ethical dilemmas associated with paid research participation, the exploitation of vulnerable groups, and the validity of the data produced.

Keywords: healthy volunteer, ethics, phase I trial, human challenge study, paid research participation, undue inducement, exploitation, serial participation, risk, deception

Introduction

Within biomedical research, healthy individuals are widely used as human subjects. Healthy people can be used to model normal physiological states for basic research or to compare with diseased patients, but they are also critical to testing drugs and vaccines. In particular, healthy individuals are widely used to assess the safety and tolerability of new therapies (phase I clinical trials), to compare generic drugs and their brand-name counterparts (bioequivalence trials), and to test the effectiveness of treatments after intentional infection with microorganisms (challenge studies of viruses, parasites, etc.). While some studies require only a few hours of healthy participants' time, others require that they consent to a confinement period of days or weeks in a research clinic. Confinement is designed to impose restrictions and controls on participants as well as to monitor their safety. Many clinical studies pose bodily risks to the healthy individuals who enroll, and a host of ethical issues arises from their involvement in research, including concerns

about undue inducement and exploitation. This chapter details why healthy individuals are valuable to biomedical research, why they enroll in studies, and the ethical problems that healthy volunteer research is meant to solve as well as the ethical issues that plague their research involvement. This chapter particularly focuses on phase I clinical trials in which healthy volunteers are used to test new drugs.

Why Are Healthy People Used in Biomedical Research?

There are at least three reasons why investigators choose to enroll healthy participants in biomedical research. First, investigators claim that healthy participants can provide clearer data about an investigational treatment because they have no underlying illness to create ambiguity in trial results. Specifically, for studies measuring the safety profile of a drug where the purpose of the study is to collect data on adverse effects, healthy participants may provide better information about which physiological changes—or symptoms and medical events—are caused by that drug (Sommer et al. 2010). A second, and related, reason that investigators choose to use healthy participants is that they believe that the risk of testing an investigational therapy is minimized compared to enrolling "affected" patients (Griffin, Posner, and Barker 2013). The idea here is that healthy individuals are better able to withstand temporary physiological changes, such as impaired kidney or liver function, whereas patients might experience serious complications from as-yet-unknown risks of a new therapy. A third reason propelling investigators to use healthy participants is that recruitment is far easier and faster for these studies compared to enrolling participants who have the illness targeted by the investigational therapy (Sommer et al. 2010). Not only does quicker accrual of participants serve investigators, but it also can help to shorten the clinical development timeline of a novel therapy, which means it could potentially (if proven sufficiently safe and efficacious) reach the market and patients sooner (Fisher 2007b). Thus, in addition to scientific reasons to design studies using healthy participants, there are economic incentives to do so.

At the same time, there are limits to what can be learned from using healthy participants in clinical research (Talbot and Stephens 2004). For safety trials, healthy individuals can provide preliminary information about the action of a drug. However, because of the well-controlled nature of these studies, the number and magnitude of adverse events are much lower than they would be among the population at large, particularly compared to patients (Corrigan 2002b). Moreover, healthy male participants often significantly outnumber female participants (Chen et al. 2018; Jain, Cottingham, and Fisher 2020). This is because many healthy volunteer trials exclude or restrict the participation of women of childbearing potential. Such restrictions are designed to limit the possibility that a fetus could be exposed to the investigational therapy (Corrigan 2002a),[1] but the absence of women from these trials means that sex-based differences of a therapy's safety or tolerability cannot be assessed as part of healthy volunteer trials (Mazure and Jones 2015). Thus, when it comes to the safety of new drugs and vaccines, additional data must be col-

lected through further studies that are conducted on patients instead of healthy participants.

Why Do Healthy People Enroll in Biomedical Research?

Healthy individuals can derive no medical benefit from their research participation (by virtue of being healthy), so they are typically offered financial compensation to incentivize their study enrollment. Nevertheless, participants are often referred to as healthy "volunteers" to emphasize their informed and non-coerced research involvement, but given that volunteering is generally assumed to be unpaid, the term can be critiqued as a misnomer (Elliott and Abadie 2008). Indeed, some clinical trials offer thousands of dollars and can provide a significant source of individuals' income (Abadie 2010; Camporesi and McNamee 2014; Fisher 2020). Healthy participants are more likely to receive large sums when they are required to spend all or part of a study confined to a research facility, such as for phase I trials (Edelblute and Fisher 2015). Beyond financial motivations to enroll, empirical studies of healthy volunteers have shown that individuals perceive other benefits from their trial enrollment, including the opportunity to learn more about and promote their health, develop friendships, and contribute to science and/or society (Fisher et al. 2018; Kraft et al. 2019; Stunkel and Grady 2011).

The extant literature on healthy people who enroll in medical research has largely focused on those who are so-called professional participants in the United States (e.g., Abadie 2010; Elliott 2008; Weinstein 2001). Considerable evidence suggests that US clinical research depends on "repeat" or "serial" participants to fill healthy volunteer trials (Fisher 2015a, 2015b; Tishler and Bartholomae 2003). For these individuals, their motivation is to use clinical trial compensation as their sole or primary source of income (Johnson 2016). In addition to providing financial support, individuals who pursue clinical trials full-time often do so because they value the flexibility and lifestyle that this economic opportunity provides, particularly by allowing them to avoid working 9-to-5 jobs (Fisher et al. 2018). Paid research participation is a form of independent contract work, but healthy participants are not classified as workers (Fisher 2019). Some bioethics commentators have argued that clinical trial participation should not be considered equivalent to work (e.g., McNeill 1997; Różyńska 2018; Stones and McMillan 2010), whereas others have advocated for treating participation as work in order to provide participants with the protections afforded by occupational health and safety laws, as well as access to workers' compensation should participants be harmed by the research (e.g., Lemmens and Elliott 1999, 2001; Abadie 2019; Malmqvist 2019).

Another reason why the field of bioethics has focused on professional participants is that many such healthy volunteers are known to prioritize their own financial gain over the scientific purpose of clinical trials (Abadie 2010). Participants are supposed to observe a "washout period" between clinical trials, but some healthy volunteers lie about their last study in order to enroll in their next study faster and thereby make more money from tri-

als in a shorter amount of time (Edelblute and Fisher 2015). Participants can do this in the United States because there is no single centralized database that tracks clinical trial enrollment (Kupetsky-Rincon and Kraft 2012; Resnik and Koski 2011). Additionally, serial participants engage in other forms of rule-breaking, such as failing to observe trial restrictions on their diet and exercise; and they also jeopardize trials by failing to report symptoms or medical events they experience during clinical trials (Fisher 2020; Monahan and Fisher 2015; Walker, Cottingham, and Fisher 2018). These behaviors have led some commentators to refer to participants as "deceptive" or "subversive" (Dresser 2013; Dickert 2013; Devine et al. 2013; Resnik and McCann 2015). Yet, the extent to which professional participants routinely undermine trials is unknown, and some empirical research suggests that some, if not many, participants are committed to following trial protocols to deliver good data to investigators (McManus and Fisher 2018; Zvonareva et al. 2019).

Regardless of the frequency of any single individual's enrollment in research, participation as a healthy volunteer appears to be profoundly shaped by social and economic inequalities (Fisher 2020). Despite assumptions that these participants are largely drawn from student populations, this has become less often the case as clinical trials are increasingly conducted not at universities but at private, commercial research clinics (Fisher 2009). While students might still make up the majority of healthy participants at universities where imaging and human infection ("challenge") studies are done (Bijker, Sauerwein, and Bijker 2016; McNeil 2017), phase I and bioequivalence drug trials more commonly enroll members of the community at large. In the United States, healthy volunteers in investigational-drug trials are typically racial and ethnic minorities (Fisher and Kalbaugh 2011; Grady et al. 2017). US African Americans and Hispanics experience more difficulty securing and maintaining stable, well-paid jobs as a result of unequal education and employment opportunities, racism, and discrimination (Kalleberg 2011; Thernstrom and Thernstrom 2009). For some members of these social groups, financial precarity makes clinical trial participation seem like the best choice to make ends meet despite the risks (Cottingham and Fisher 2016; Monahan and Fisher 2020; Williams and Fisher 2018). Thus, it is important to underscore that financial motivations to enroll in research differ depending on the healthy person's social and economic position, which consequently might determine whether that person should be perceived as vulnerable in the context of research (Fisher 2013).

What Are the Ethical Justifications for Using Healthy Volunteers in Research?

Although healthy participants are exposed to risk without the possibility of personal medical benefit, investigators and research ethics boards often argue that it is *more* ethical to do research on healthy volunteers than on patients. One such reason returns to the issue that investigators believe that healthy individuals' bodies are less vulnerable to harm compared to those of patients (Griffin, Posner, and Barker 2013). From this standpoint, the use of healthy volunteers protects patients from research harms, and this reasoning

has parallels with narratives of why nonhuman animal research must be done prior to any human testing (see also Fisher and Walker 2019). Healthy volunteers, therefore, are constructed as serving as more robust—and therefore ethically appropriate—research subjects to investigate unknown safety concerns that might emerge.

Additionally, some researchers subscribe to the view that when a treatment's efficacy is not the purpose of a trial, it would be a misuse of patients to enroll them in that type of clinical research (e.g., Sommer et al. 2010). The logic of this perspective rests on patients being a scarce resource and that enrolling them in one trial effectively eliminates them from another. Thus, enrolling patients in safety trials could potentially make it more difficult to secure participants for efficacy trials.[2] From an ethics perspective, then, one could argue that the use of healthy volunteers helps to ensure that patients are enrolled in research when they are most needed, which could result in therapies getting to the market faster. In other words, this view creates a participant division of labor in research, in which patients should be enrolled in clinical research that actually has the potential for direct medical benefit rather than for nontherapeutic, safety trials. However, subscribing to this ethical rationale depends on a holistic accounting of clinical research in which different groups of participants' relative value to the research enterprise needs to be leveraged to achieve the most ethical result.

Another ethical justification for using healthy volunteers in research is that they are very unlikely to suffer from a therapeutic misconception. Recall that such a misunderstanding of the research means that someone falsely believes that they will benefit medically from their trial participation (Appelbaum and Lidz 2008). Ample empirical research has demonstrated how patients are likely to interpret their research involvement as a form of treatment (e.g., Henderson et al. 2006; Dresser 2002). Such therapeutic misconceptions are particularly troubling for clinical research that cannot benefit the participants, such as when the trials are designed to test a product's safety and tolerability (Resnik 2001). Likewise, patients might be under the impression that their own physicians recommend a clinical trial as their best treatment option, rather than perceiving the possibility that their providers have a financial conflict of interest in enrolling patients as participants (Klein and Fleischman 2002). To avoid the possibility of a therapeutic misconception in such trials, healthy volunteers might be positioned as the ideal participants. Without an illness or disease for which they are seeking treatment, healthy volunteers understand that the clinical trial is not aimed at providing medical treatment or improving their health. To the extent that this means that healthy volunteers are better informed about the potential benefits (or lack thereof) of their participation, their involvement in research can resolve some ethical concerns that emerge.

What Are the Ethical Concerns Associated with Using Healthy Volunteers in Research?

Despite any ethical rationales for using healthy volunteers in biomedical research, there are also serious ethical issues that emerge from their involvement in research. Four such concerns regularly discussed in the literature involve exposure to risk, undue inducement, exploitation, and invalid trial data. Although these ethical concerns potentially arise in all clinical research, the use of healthy volunteers triggers dilemmas that differ from research on patient populations.

Risk of research participation is a tricky issue in healthy volunteer research. Risks to participants of all research must be appropriate and minimized through the research design, but no clinical trials, including those using healthy volunteers, are completely risk-free (Chapman 2011). Ethics boards are charged with determining that the risk–benefit ratio justifies the research, wherein the risk is typically to the participants themselves while the benefits might not be for the individuals enrolled but for society more generally (Faden and Beauchamp 1986). Additionally, US regulation prohibits ethics boards from considering financial compensation as a "benefit" that can justify or offset risk (US Food and Drug Administration 2018). From an ethical standpoint, this is an important aspect of the review of research protocols; otherwise, any risk might be deemed appropriate provided research participants were sufficiently compensated financially. Despite this perspective on formal research benefits, participants themselves indeed engage in their own risk–benefit analysis to determine whether financial compensation is worth the risk (or inconvenience) of research enrollment (Fisher, Monahan, and Walker 2019; Kraft et al. 2019). Nonetheless, other factors must be in place to balance the risks and benefits of healthy volunteer research.

Given that healthy volunteers cannot themselves benefit medically, how can risks be judged appropriate in this type of biomedical research? Risks are typically minimized through trial designs that emphasize a conservative approach to exposing healthy volunteers to risk. Specifically, in drug trials, the protocols often utilize a dose-escalation design that establishes starting doses of the investigational drug at levels deemed to be pharmacologically inert, and subsequently higher doses of the drug are administered only after investigators have judged the lower doses to have been safe for participants. In some first-in-human trials, investigators also employ "sentinel" dosing in which only a single participant receives the investigational drug (and a second participant receives a placebo) to ensure that no unexpected and life-threatening responses to a drug could occur to an entire cohort of participants (van Gerven and Bonelli 2018). Beyond dosing, the restrictions on healthy volunteers' activities also contribute to minimizing their risk. As already stated, confinement in a research clinic is a key component in managing risk to healthy volunteers (Karakunnel et al. 2018). Confining participants is particularly important in human challenge studies (when healthy participants are intentionally exposed to a microorganism) because they can be monitored during the study but also managed to

avoid infecting others by not allowing participants to be among the population at large until it is safe to resume their normal routines (Bijker, Sauerwein, and Bijker 2016).

Healthy volunteer clinical trials are largely thought to be very safe. Specifically, meta-analyses of phase I drug trials on healthy volunteers have shown that adverse events are quite common (occurring in roughly 65% of participants) but that only 1%–4% of these adverse events are deemed serious (Sibille et al. 1998; Johnson et al. 2016; Emanuel et al. 2015). Further, most adverse events are short-term and resolve without any medical intervention on the part of the investigators. Despite these trials' safety record, death and severe injury to healthy volunteers remain possibilities. At least three deaths have occurred since the turn of the century. In 2001, Ellen Roche, a 24-year-old, died in an asthma-related study at Johns Hopkins University (Kolata 2001). Then in 2004, Traci Johnson, a 19-year-old, committed suicide during an antidepressant study at Eli Lilly's Indianapolis research clinic (Harris 2004). More recently, Guillaume Molinet, a 49-year-old, was declared brain-dead after participating in a 2016 analgesic study in Rennes, France (Hawkes 2016). That same clinical trial also resulted in the long-term neurological impairment of three other healthy volunteers. Another dramatic case of injury to healthy volunteers occurred in London in 2006 when six participants nearly died from a minute dose of an investigational immunotherapeutic drug that unexpectedly caused rapid multiple organ failure (Wood and Darbyshire 2006). The London trial led to the European Union adopting new safety measures for clinical trials, including requirements to conduct sentinel dosing for first-in-human trials (van Gerven and Bonelli 2018), but the death and injuries in France indicate that research tragedies happen even with these additional safeguards in place. The death of and/or long-term harm to healthy volunteers is a particularly fraught ethical concern because these research participants accept bodily risks without the possibility of direct medical benefits.

Another important part of the question about risk to healthy participants pertains to whether serial participation may produce long-term health effects. Unlike existing meta-analyses that seek to determine how risky individual phase I trials typically are, there have been no empirical studies examining how ongoing enrollment for months, years, or even decades might affect participants' health. Moreover, there is consensus that risk might be exacerbated when participants fail to follow trial protocols, but investigators have been shown to be complicit in healthy volunteers' rule-breaking, for example, by allowing participants to enroll in trials when they suspect they have not observed washout periods.[3] Yet, the importance of strictly following the research protocols is unclear for determining how and when participants might be increasing their risk of being harmed. To date, no investigations have tied the incidence and/or prevalence of adverse events to various forms of rule-breaking in which healthy volunteers might engage.[4] Thus, for some segment of healthy volunteers, the risks of their participation in biomedical research might be more significant than for individuals who enroll in only one single trial and observe all the protocol restrictions.

Related to questions of risk are ethical concerns over undue inducement in healthy volunteer research. Undue inducement has been taken up in more detail elsewhere in this volume (see Phillips), but healthy volunteer research proves a particularly vexing context for ensuring that participants' decisions to enroll have not been unduly influenced by incentives. Specifically, the concern about undue inducement is that participants will be unable to evaluate appropriately the risks of research because of their desire to receive whatever has been offered to them in exchange for their participation (Halpern et al. 2004; Grady 2005). In the case of healthy volunteers, the inducement would almost always be the offer of financial compensation. What makes the determination of "undue" versus "appropriate" inducement so difficult in the context of healthy volunteer research is that the amount at which someone's decision to enroll might be inappropriately swayed will vary based on their social and economic context (Gelinas et al. 2018). In other words, a set amount of money does not have the same value to everyone to whom it is offered. Because of this, scholars have also voiced concern that by setting compensation too low, investigators might largely avoid undue inducement, but they will end up enrolling only the lowest-income individuals, for whom smaller stipends are nonetheless attractive (Dunn and Gordon 2005). In other types of biomedical research, investigators could choose to avoid the ethical dilemma altogether by not offering any form of payment or compensation for participation or by keeping the amount at a level that merely reimburses people for expenses they incur (e.g., travel to the clinic). However, healthy volunteer trials are largely believed to *require* financial compensation to get anyone to enroll. When the research relationship is predicated on the inducement offered, it becomes all the more difficult to find the line at which a certain dollar amount alters someone's ability to judge the risks.

There is a lack of consensus in the bioethics literature about undue inducement in healthy volunteer research. Empirical research has certainly confirmed that participants are motivated to enroll by the offer of money, but existing studies offer less conclusive evidence about when and how people's decision-making might be distorted by the compensation. On the one hand, some studies seem to confirm that participants do not appropriately account for risks when offered large amounts of financial compensation. For example, a study found that healthy volunteers exhibited "poor quality decision making" about a clinical trial, and the authors attributed that finding to the financial compensation (Rabin and Tabak 2006). Another study underscored that healthy volunteers might disregard study risks when they feel that the risk of not earning any income is the greater threat in their life (Cottingham and Fisher 2016). On the other hand, studies have also found that healthy volunteers appear to be well informed about and quite rational about research risks. A survey conducted by Grady and colleagues (2017) found that healthy volunteers ranked risks as more important than the amount of money offered when making enrollment decisions for phase I trials. That study's findings also indicated that healthy volunteers can and do "shop around" for a clinical trial based on myriad factors, including risk (Grady et al. 2017; see also Fisher, Monahan, and Walker 2019). Thus, evidence about the extent to which monetary compensation can serve as an undue inducement for healthy volunteers is mixed.

A complementary ethical issue surrounding payment for research participation involves concern about exploitation (Phillips 2011). By keeping payment low, investigators and ethics boards may be contributing to the exploitation of the most economically disadvantaged groups (Iltis 2009; Largent and Lynch 2017). Evaluating exploitation depends, in part, on whether the people who bear the burdens of research are able to reap its benefits. In the case of biomedicine, those with the fewest economic resources are also unlikely to have access to the best healthcare. This is all the more true in a country like the United States that does not have universal healthcare and where the cost of medical therapies such as pharmaceuticals is extraordinarily high, even for those individuals who have private insurance (Fisher 2009). Yet, because healthy individuals do not need access to medical interventions, there is no easy fix to this issue.[5]

Not all commentators agree that all forms of exploitation in research are equally unethical. For example, Wertheimer (1999) developed the concept of "mutually advantageous exploitation" to illustrate how there are circumstances in which research participants can still benefit from what could be classified as exploitative research. From his perspective, it is more acceptable to allow exploitation in these cases because the exploited receive something they would not otherwise. Applying this to healthy volunteer research, one could argue that the biomedical research enterprise is not responsible for the profound economic inequalities that can be said to create willing participants (Fisher 2007b), so the offer of monetary compensation has a net benefit of contributing to their well-being. This framing of mutually advantageous exploitation is even persuasive to research participants (Walker, Cottingham, and Fisher 2018). While many healthy volunteers are critical of the enormous profits that pharmaceutical companies make from products that depend upon research participants' contribution to drug development, they often also feel as though the monetary compensation largely benefits them (Fisher 2020). They might also argue that they should be paid more for their participation, but they feel better off for the opportunity to enroll in research. However, there are social justice concerns that emerge when certain demographic groups—such as racial and ethnic minorities—are disproportionately used in research with few direct benefits to them (Fisher 2007a).

The topic of how much healthy volunteers—or any research participants—*should* get paid is quite fraught. As should now be clear, investigators are asked to thread the needle between undue inducement, on the one hand, and exploitation, on the other (Phillips 2011). Payments are often based on what appears to be the going rate for research participation in a specific locale (Dickert and Grady 1999). This could ultimately be arbitrary or based on finding the lowest rates possible that will not impede recruitment. Other payment models include paying people according to their own hourly wages, thereby creating a scale that would offer different levels of compensation to participants in the same study based on their individualized income (Dickert and Grady 1999). Healthy volunteer trials often commonly include "completion bonuses" that incentivize participants' retention in a study by withholding a sizeable portion of the compensation and giving it only to those participants who complete all the study visits (Largent and Lynch 2019). Despite the large amount of ink that bioethics scholars have spilled on the topic of payment for re-

search, there remains no consensus around or persuasive position on what is a truly fair way to compensate participants for their involvement in research.

Although payment—and its ties to undue inducement and exploitation—is one of the primary ethical concerns that emerges in healthy volunteer clinical trials, it tends to overshadow equally important and complementary problems that are endemic to this type of biomedical research. Empirical studies have uncovered instances in which participants' powerlessness to set the terms of the exchange in research leads to ethically problematic treatment of healthy volunteers (Johnson 2016; Walker, Cottingham, and Fisher 2018). As one such example in phase I trials, clinics typically overenroll healthy volunteers. The clinics' aim is to ensure that they have the total number of participants needed for a study, so they guard against individuals' exercising their right to decline participation after they consent but before the trial begins, as well as against evidence that not all participants will pass the slew of medical check-in tests that would qualify them for the study (e.g., blood pressure readings, kidney and liver function tests, illicit drug screen, etc.). However, healthy volunteers' participation commitments can include taking time off of work for the entire confinement period or traveling hundreds or thousands of miles to the research clinic, yet they still risk being told that they are not needed for the study (Fisher 2020). There is no right to participate in research only to decline participation, but when healthy volunteers are told they are not needed because the clinic has overenrolled the study, this situation advantages the research clinics at the expense (sometimes quite literally) of the participants (Walker, Cottingham, and Fisher 2018). Thus, research participation includes many burdens that have received much less ethical analysis than the question of payment or health risks.

A final ethical issue raised in the literature concerns the validity of results from clinical trials using healthy volunteers. As already touched upon briefly, there are limits to how well healthy bodies can provide relevant data about drug safety for diseased populations (Fisher 2020). More concerning is the possibility that serial participants are unrepresentative of the general population either because they have been exposed to a range of investigational products or because those who continue to enroll have a higher tolerance for or less sensitivity to novel chemical compounds (Sibille et al. 1998). Beyond the physiological features of healthy volunteers, when those "subversive subjects" lie about their medical histories, prior clinical trial enrollment, and experiences of adverse events, the resulting clinical trial data are thrown into doubt (Dresser 2013; Resnik and McCann 2015). The validity of the data produced using healthy volunteers is an ethical issue because there might be increased risk to patients from these products once they are available on the market. Emphasizing the seriousness of this issue is the frequency with which postmarketing safety problems emerge once patients are prescribed new drugs (Downing et al. 2017; Pinnow et al. 2018).[6]

Conclusion

The use of healthy volunteers is a fundamental part of the biomedical research enterprise, and current regulatory requirements for testing the safety of new drugs ensure that healthy volunteers will continue to be used in clinical trials. As this chapter has shown, there are arguments advanced in the literature both advocating for why the use of healthy volunteers diminishes ethical concerns in research as well as cautioning how healthy individuals' involvement in research raises thorny ethical issues. However, it would be a mistake to believe they balance out. While there might be justifiable scientific and ethical reasons to use healthy individuals in research, the current political and economic context for their enrollment means that paid research participation creates more ethical problems than it solves (Fisher 2013). As ample empirical research has shown, social inequalities motivate much research participation among healthy volunteers in the United States and around the world (Fisher 2020; Rajan 2007; Cooper 2008). As a consequence, attention to research ethics requires the field of bioethics to consider how individuals are vulnerable to exploitation and exposed to risk for the purpose of expedient—but possibly invalid—science.

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Notes:

(1.) For many investigational drugs and vaccines, human trials commence before nonhuman animal studies are completed. In particular, reproductive toxicity studies have often not been done prior to human trials, so the effects of the investigational agent on fetal development are unknown. Without animal data suggesting that there would be no fetal harm, investigators opt to exclude women of childbearing potential from studies (Parkinson, Thomas, and Lumley 1997). In this way, investigators and pharmaceutical companies prioritize the protection of hypothetical fetuses over the acquisition of data about sex-based drug responses (Corrigan 2002a; Fisher and Ronald 2010).

(2.) An important exception to the use of patients in safety trials is oncology phase I trials. These safety trials often enroll cancer patients who have exhausted their other treatment options. While enrolling in a phase I trial is not seen as therapeutic for cancer pa-

tients, the trials often do simultaneously collect preliminary data on a therapy's potential to shrink a tumor (Adashek et al. 2019). These clinical trials nonetheless generate ethical concerns regarding patients' expectations of benefit (Anderson and Kimmelman 2014; Miller 2000).

(3.) Without a single centralized database that tracks study enrollment, investigators typically have to ask participants the date of their last clinical trial. In at least some instances, the information that participants provide is contradicted by the physical evidence of trial participation on their bodies. Research staff have noted fresh venipuncture marks on healthy volunteers' arms and adhesive from electrocardiograms on their chests (Fisher 2020). Nonetheless, research staff often do not feel as though it is their right or duty to challenge the information that participants give them. While ignoring washout periods helps healthy volunteers earn more money from clinical research, it also facilitates recruitment, lessening the barriers to clinics of filling their studies.

(4.) Of course, it would be challenging to do such a study unless healthy volunteers were honest about the specific ways in which they failed to follow or blatantly disregarded trial protocols. It might take independent investigators to carry out such a study. They would have to guarantee participants' confidentiality in order to collect data on rule-breaking, but this would raise other ethical questions about what their responsibility was to report behavior that they believed jeopardized healthy volunteers' safety or undermined the validity of the clinical trials in which those healthy volunteers had participated.

(5.) In research on patient populations, some have argued that investigators should provide post-trial access to healthcare, including, but not exclusively, access to an investigational drug, in order to make clinical trials in resource-poor contexts more ethical (Sofaer and Strech 2011). In this way, exploitation of disadvantaged groups would be mitigated by their access to medical care beyond the constraints and time period of a research protocol. In the case of healthy volunteer research, there is no analogous "benefit" that could be extended to participants.

(6.) It should be noted that even trials on patients have limited ability to discern all the safety issues that can emerge from an investigational drug. Many serious adverse reactions are quite rare and only manifest (or can be shown to have been caused by the therapy) once a product has been approved for the market and is widely used in clinical practice. Depending on the nature of these adverse reactions, a product might be removed from the market altogether or subject to more labeling requirements about its safety profile and risks. One study on drugs approved for the US market indicated that one-third of these products generated sufficient adverse reactions to lead to safety communications, black-box warnings, or market withdrawals (Downing et al. 2017).

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