

# Serial Participation and the Ethics of Phase 1 Healthy Volunteer Research

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*Phase 1 healthy volunteer clinical trials—which financially compensate subjects in tests of drug toxicity levels and side effects—appear to place pressure on each joint of the moral framework justifying research. In this article, we review concerns about phase 1 trials as they have been framed in the bioethics literature, including undue inducement and coercion, unjust exploitation, and worries about compromised data validity. We then revisit these concerns in light of the lived experiences of serial participants who are income-dependent on phase 1 trials. We show how participant experiences shift attention from discrete exchanges, behaviors, and events in the research enterprise to the ongoing and dynamic patterns of serial participation in which individual decision-making is embedded in collective social and economic conditions and shaped by institutional policies. We argue in particular for the ethical significance of structurally diminished voluntariness, routine powerlessness in setting the terms of exchange, and incentive structures that may promote pharmaceutical interests but encourage phase 1 healthy volunteers to skirt important rules.*

**Keywords:** *exploitation, phase 1 healthy volunteers, research risks and benefits, structural coercion, undue inducement*

## I. INTRODUCTION

Biomedical research using human subjects is an inherently risky enterprise, which has been seen as justifiable only when risks are both minimized and reasonable with respect to overall benefit of the research for the subject or society (National Commission 1979; 45CFR46). Undertaking such risks must also typically be voluntarily agreed to by participants (through their informed consent) and the risks of research must not disproportionately fall on socially disadvantaged, or otherwise vulnerable, groups without the potential for balancing benefits (National Commission 1979; 45CFR46). Phase 1 healthy volunteer clinical trials—those research studies that financially compensate subjects in tests of drug toxicity levels and side effects—appear to place pressure on each joint of the moral framework justifying research: the risk-benefit trade-off and how to understand the acceptable role of payment, the adequacy of informed consent to such participation, and the potential for economic vulnerability of the participants.

In this paper, we review three logically distinct, but intertwining, lines of argument that run through the bioethics literature concerned with the ethics of phase 1 clinical trials: undue inducement and coercion as undermining voluntary participation; the unjust exploitation of an economically vulnerable population; and worries about compromised data validity undermining the overall risk-benefit profile of the research. We then revisit each set of concerns in light of the lived experiences of serial participants who are income-dependent on phase 1 trials. To illustrate these experiences, we rely on case studies of five representative individuals participating in the HealthyVOICES project, a longitudinal study of 180 healthy volunteers participating in phase 1 research in diverse clinics across the United States. We opted for a case study approach, rather than reporting on all the participants in our study, because it allows us to delve more deeply into the lives and complex perspectives of healthy volunteers.

By combining our analysis of the moral concerns of phase 1 research with the perspectives of healthy volunteers, we illustrate how bioethical approaches can sometimes miss the larger structural and system-oriented problems that pervade this realm of research. In particular, we argue that attending to the population most at risk in phase 1 trials (i.e., serial participants dependent on study income) refigures relevant bioethics debates. Specifically, these phase 1 participant perspectives shift attention from discrete exchanges, behaviors, and events in the research enterprise to the ongoing and dynamic patterns of serial participation in which individual decision-making is embedded in collective social and economic conditions and shaped by institutional policies. In so doing, their concerns and experiences allow for innovative perspectives on voluntariness, justice, and balancing risk of harm and potential for benefit for this research group. We specifically investigate: (1) structurally diminished voluntariness in light of

serial volunteers' background social contexts and lack of information about the health impact of repeat trial participation; (2) experiences of routine powerlessness in response to clinical trial clinic policies as an alternative to, or component aspect of, exploitation; and (3) incentive structures that may advantage trial sites and promote pharmaceutical interests, but encourage phase 1 healthy volunteers to skirt important rules that protect safety and data validity. Our goal in contributing these observations is to encourage more fruitful debates over phase 1 research by engaging the concerns of serial participants.

## II. THREE WORRIES ABOUT PHASE 1 HEALTHY VOLUNTEER RESEARCH

There is no question that people have died or been seriously harmed by their participation in phase 1 healthy volunteer research (Steinbrook, 2002; Lenzer, 2005; Honey, 2006; Bégaud et al., 2016). However, the overall risk of serious adverse events has been estimated to be very low (Sibille et al., 2006; Lutfullin, Kuhlmann, and Wensing, 2005; Kumangai et al., 2006) in spite of healthy volunteers facing *some* risk of serious harm in addition to the experience of more common side effects such as headache, diarrhea, skin rashes, etc. (Lutfullin, Kuhlmann, and Wensing, 2005; Fisher, 2015a). Because these volunteers are otherwise healthy, they gain no direct medical benefit from research participation. Such participation, moreover, involves uncomfortable procedures (typically repeat blood draws, but less common procedures include bronchoscopy or lumbar puncture), causing at least one participant to refer to phase 1 healthy volunteer research as the “mild torture economy” (Abadie, 2010, 2). Additionally, these trials are time-consuming. They usually occur in a “confinement” facility where volunteers must remain for some portion, or the entire duration, of the study (anywhere from days to weeks) and be subjected to strict dietary schedules and other substance and product prohibitions (Fisher, 2015a). Not surprisingly, volunteers are induced to participate through financial incentive, generally in the range of \$100 to \$300 per day (Edelblute and Fisher, 2015). Importantly, healthy volunteers are typically “repeat” participants enrolling serially in phase 1 trials (Tishler and Bartholomae, 2003; Kass et al., 2007; Abadie, 2010; Fisher, 2015a, 2015b). In spite of the prevalence of serial participation, there is currently no single centralized database or registry in the United States to track the participation of healthy volunteers and to prevent simultaneous enrollment in multiple trials (Kupetsky-Rincon and Kraft, 2012; Edelblute and Fisher, 2015).

The very idea that a biomedical research study's profile of risk and potential to benefit may be justified by interpersonal rather than intrapersonal calculations may seem ethically dubious. Is it really the case, we might ask, that risk to subjects who will not themselves benefit can be offset by the potential

for benefit to others? As we have already noted, this moral premise has been sustained in the US regulatory structure guarding human subject research by stipulations to minimize risk as well as the safeguards of informed consent and the just selection of participants. The practice of offering payment to encourage healthy individuals to participate in phase 1 research further complicates this picture, since payment straightforwardly benefits participants, yet such “benefit” should not be taken into account by ethics review boards to justify the research itself because this would problematically skew an appropriate assessment of potential harms and benefits (US National Institute of Health, 2005; US Food and Drug Administration, 1998). In the extreme, using such a model, a study with medical risk and no promise of medical benefit could be ethically justified solely by the financial compensation of the subjects.

Some early commentators worried that any incentive other than authentic identification with the scientific goal was a morally problematic basis for research participation (Jonas, 1969) and that offering payment for research participation could be coercive and should not be counted as benefiting subjects (Macklin, 1981; 1989). However, the current “uneasy compromise” (Elliot, 2008, 40) over payment for phase 1 participation recognizes that such payment is both the incentive driving participation—and in that sense clearly benefits participants—and yet, from a research oversight perspective, ought not to figure into the overall justification for the research (i.e., as a counterbalance to risk in ethics review board approval). Despite a relatively wide acceptance of this uneasy compromise over how to accommodate payment within phase 1 research, concerns over such payments being both too low and too high abound in the literature as posing (somewhat conflicting) potential problems for informed consent and justice. An emerging set of concerns focuses on whether research results are compromised by the kinds of behavior promoted by paying for participation. We briefly introduce each worry in turn.

#### Compromising Voluntariness: Undue Inducement and Coercion

In their review of US human subject research, institutional review boards (IRBs) are cautioned by the federal regulatory structure to be on the lookout for both “undue influence” and “coercion” that might undermine voluntary consent (Department of Health and Human Services, 2009, 45CFR46, section 46.116). Bioethics scholars, however, have been careful to limit the application of the term “coercion” to exchanges that involve a wrongful threat of harm or force as a means of extracting particular behaviors or responses and have claimed, in particular, that genuine offers cannot be coercive (Wertheimer and Miller, 2008; Wilkinson and Moore, 1997; Hawkins and Ezekiel, 2005). Indeed, the tendency of IRBs (and perhaps members of the general public) to think of coercion as simply an extreme of undue

influence (Klitzman, 2013; Largent et al., 2013) has been roundly criticized by these scholars who write that “[if] IRB members’ concerns are based on conceptual or ethical misconceptions, unnecessary limits may be placed on payments to research participants and impede valuable research” (Largent et al., 2013, 500–1). The lesson is that, “Genuine offers do not coerce. Period.” (Wertheimer, 2011, 144).<sup>1</sup>

Putting to bed worries that payments may be coercive, bioethics scholars have attended with much greater concern to the question of whether payments may undermine voluntariness by unduly influencing potential participant’s decision-making. But, what is meant by “undue” influence? Multiple commentators have noted that inducing participation through payments is not *prima facie* problematic (if it were, the critique would extend too broadly—for example, to paying people to work at risky jobs) (see Wilkinson and Moore, 1997). Agreement within the bioethics literature seems to have coalesced instead around the notion that undue inducement somehow “triggers irrational decision-making” (Wertheimer, 2011, 149; Largent et al., 2013; Ballantyne, 2008; Philips, 2011). In particular, the distortion of judgment for which we must be on the lookout is an “under-estimation of risks and an over-estimation of benefit” (Philips, 2011, 213).

In this context, the difficulty that remains is the question of how much financial incentive constitutes an “undue” influence or what economic model should become the referent for how and why to provide money in exchange for research participation (VanderWalde and Kurzban, 2011). IRBs are typically left to come up with their own norms about what compensation rates are ethically appropriate, creating wide variation across research institutions (Dickert and Grady, 1999). In spite of concerns about undue inducement, some commentators argue that researchers must account for market forces and compensate more generously to ensure fairness in compensation as well as a more diverse pool of prospective participants (Dunn and Gordon, 2005).

#### Undercutting Justice: Exploitation of the Economically Vulnerable

To lessen the possibility that an offer is so “attractive that [it can] blind prospective subjects to potential risks or impair their ability to exercise proper judgment about the risks of participation” (IRB guidebook, as cited in Wertheimer, 2011, 149), there is general agreement that payments for research participation should be restricted. However, the practice of offering low payments for such participation has spurred a different kind of bioethical worry—namely, the potential for exploitation of the economically vulnerable. The moral tension between concerns of undue influence on one hand and exploitation on the other has been widely recognized in the bioethics literature (see Macklin 1989; Ballantyne 2008; Phillips 2011) and is readily summarized by Ballantyne (2008, 179) who writes, “offer participants

too little and they are exploited, offer them too much and their participation may be unduly induced.”

Although exploitation is generally seen in the literature concerned with payment for study participation as a matter of “unfairness of the distribution of benefits and burdens between the parties to a transaction” (Ballantyne 2008, 180), there is little consensus about whether such unfair distribution itself offers moral reason to interfere in the relevant exchanges. Unlike in cases of exploitation where one party does not (or cannot) consent or does not benefit, when “a consensual and mutually advantageous transaction” (Wertheimer 2011, 177) results in one party paying too much or receiving too little, Alan Wertheimer (2011, 253) has proposed that there are no clear moral grounds for interference in the exploitative exchange. Whether or not that is the case, several commentators less impressed by concerns of undue influence than exploitation of the economically vulnerable have argued for establishing minimum thresholds on healthy volunteer payments and/or not putting any upper limit on such payments (see, e.g., Shamoo and Resnik, 2006; Phillips, 2011).

#### Disrupting the Risk-Benefit Justification: Data Validity and Subversive Behavior

An emerging concern about payment for healthy volunteer phase 1 trial participation is that such payment creates incentives for problematic participant behaviors that may undermine data validity. Undermining data validity in turn disrupts the trial justification that depends on an accurate assessment of the potential for benefit and likelihood of harm. Examples of such disruptive behaviors include not adhering to 30-day “washout” periods between studies; dishonesty about ingestion of other prescription, over-the-counter, or illicit substances; failing to ingest study drugs; providing false medical or other history; and not following the required study diet. Although several commentators have expressed concern that paying subjects for their participation will incentivize problematic behaviors such as these (see, e.g., Tishler and Bartholomae 2003; Shamoo and Resnik, 2006; Resnik and Koski 2011), Rebecca Dresser has offered the most thorough assessment of the moral dimensions of the problem. She concludes,

Subversive subjects present a serious threat. Their behavior reduces the validity of trial results, with potentially harmful consequences to patients and to subjects participating in subsequent trials. Subversive subjects also expose themselves to heightened research risks. (Dresser 2013, 832)

In this section, we have reviewed three distinct, but somewhat interrelated sets of ethical concerns about phase 1 healthy volunteer research raised within the bioethics literature. Next, we describe the HealthyVOICES project,



provide details about the approach we have taken in this paper, and introduce the participants who will serve as our informants in both assessing and complicating these common concerns.

### III. PROJECT OVERVIEW AND METHODOLOGICAL APPROACH

Presumably, the ethical worries about healthy volunteer research raised in the bioethics literature are particularly significant for those participants most at risk in phase 1 trials—serial participants who are dependent on study income. In response to the dearth of information about how healthy volunteers perceive the risks and benefits of phase 1 trials, as well as how they make decisions about their participation, we designed a longitudinal study to shed light on these ethical and empirical concerns. The study, the HealthyVOICES project, recruited healthy volunteers when they were participating in a clinical trial at one of seven phase 1 clinics across the United States. For healthy volunteers who consented to participate in our study for a three-year period, a member of our research team conducted a “baseline” semi-structured interview with them in the phase 1 clinic. Participants were then randomized to a “full participation” or “control” arm of the study, with roughly 80 percent of all enrolled participants being allocated to the full participation arm. As part of the protocol for the full participation arm, participants consented to four additional follow-up telephone interviews, taking place six months, one year, two years, and three years from their enrollment in our study. Those participants also agreed to report all of their phase 1 clinical trial activity to us over the course of their three-year involvement in our study (see [Edelblute and Fisher, 2015](#)). As part of the protocol for the control arm, participants consented to one additional interview three years from enrollment as well as periodic check-ins to ensure that their contact information was current. The goal of the control group was to have a mechanism to assess whether participation in our study had an overall effect on their perceptions of or decisions about phase 1 trials.

We enrolled a total of 180 healthy volunteers in our study. As part of our recruitment process, we selected phase 1 clinics across the United States in order to have a demographically diverse sample of healthy volunteers. As previous studies have indicated, phase 1 healthy volunteers tend to be primarily men and drawn from low-income, minority groups with greater representation of African Americans in the Eastern and Midwestern United States and of Hispanics in the Western United States (see, e.g. [Fisher and Kalbaugh, 2011](#); [Fisher, 2015a](#)). Our final sample mirrored these national trends with 72.8 percent of our participants being men and 60.5 percent being members of minority groups (40.5 percent black; 20.0 percent Hispanic). We collected additional data at baseline about their experience participating in phase 1 trials as well as more customary demographic information. Reinforcing

the idea that phase 1 participants are typically repeat volunteers or “serial participants,” more than half of the participants had completed at least five phase 1 trials and a quarter had completed between 11 and 200 studies, whereas only 20 percent were in their first clinical trial at the time of enrollment in our study. Indicating risk of serial participation even for those volunteers new to phase 1 trials, participants were largely underemployed or unemployed (16.9 percent report full-time employment). The majority of participants had not earned a college degree, with 28 percent holding a high school diploma, GED, or less education; 29 percent had taken some college courses; and 11 percent had technical or vocational training. Twelve percent had an associate’s degree and 21 percent had a bachelor’s degree or higher. Most participants (63 percent) were between the ages of 30 and 49, 22.5 percent were between the ages of 18 to 29, and 15 percent were 50 or older.

### Case Study Selection and Analysis

Semi-structured interviews aimed to gather stories about the experiences of healthy volunteers that could provide insights into longstanding bioethical concerns or raise awareness of otherwise invisible ethical problems with phase 1 trials. For this analysis, we drew from those interviews conducted with all participants at baseline and our full participation arm at six months and one year from enrollment.<sup>2</sup> Our approach to empirical research in bioethics comes from an interpretive tradition, which combines both deductive and inductive technique of data collection and analysis (Timmermans and Tavory, 2012; De Vries and Fisher, 2013). This means that we included questions in our interview guides that were relevant to bioethical concerns on which we believed healthy volunteers could shed light from their standpoint as phase 1 participants. For example, we asked questions about their motivations to enroll in phase 1 trials (baseline), perceptions of trial compensation, including the relationship between payment and risk (baseline and 1-year), perceptions of the risks and benefits (baseline, 6-months, 1-year), their preferences about which studies in which to enroll or avoid (baseline), and their adherence to study rules and procedures (baseline). With a semi-structured interview approach, we also were able to encourage new themes to emerge, based on the participants’ experiences and perceptions of phase 1 trials. For example, participants told us across all three interviews about the economic and personal challenges they have faced in their lives, the difficulties they have encountered enrolling in trials, their worries about the long-term effects of their trial participation, and their criticism of the capitalistic nature of the pharmaceutical and clinical trials industries.

In this paper, we draw on the voices of five illustrative participants as informants whose perspectives complicate the bioethical concerns introduced above. Using case studies instead of the entire data set allows us to provide greater context for the perceptions of each participant, as well



as present their backgrounds and life circumstances as critical data for our analysis (Yin, 2003). In line with case study research, our aim in the analysis is to revisit theoretical concepts, here bioethical arguments related to phase 1 trials, rather than report statistically representative findings (Yin, 2003). We selected five participants who holistically addressed all the themes of this paper (whereas other participants in our study might voice concerns only about a smaller set). To identify these participants, we met several times to discuss the themes in the bioethics literature, the challenges to these themes that had emerged through our engagement with participant perspectives, and consider potential participants as phase 1 study informants. As we identified potential individuals, we then re-read the transcripts for each of those participants to make a final determination on whom to include. As a group, these participants are representative of our sample more broadly when it comes to their perceptions of phase 1 trials, their decision-making regarding studies, and their behaviors surrounding their participation. Another key part of our selection process was ensuring that the participants' demographic features generally reflected the entire sample in terms of representation by age, gender, race, and educational attainment. Given our interest in experienced, healthy volunteers, we intentionally excluded first-time phase 1 participants from the case studies. We did, however, include a participant in his second clinical trial in order to capture the perspective of someone newer to phase 1 participation who is at risk for serial participation based on employment status. In the remainder of this section, we introduce our informants, and in the next section we consider how their concerns and perspectives give us reason to re-frame the bioethical debates.

### The HealthyVOICES Project Participants

*Bree*<sup>3</sup> is an African-American woman in her late 30's who identifies as self-employed through clinical trials (she estimates she has participated in over 40 studies since her first in 2007). She holds a bachelor's degree and has a history of employment in what she defines as "corporate America." She enjoys the flexibility of participating in clinical trials as compared to the jobs she has held in the past. However, she wrestles with time away from home and the impact this may have on her three children. She expects to quit trials and go back to a "9 to 5" job, but currently the money from studies is too good to pass up. She participated in four additional clinical trials during the first year of our study.

*Calvin* is an African-American man in his late 30's who estimates that he has participated in "hundreds" of clinical trials since his first one in 1999. He has some college education and also works part-time in maintenance at Wal-Mart. He is living with his partner and her two children, whom he also views as partly his responsibility. He seems somewhat burned out from doing so many studies—he didn't expect to still be participating in them in his 30's.

However, he has no plan to stop re-entering what he terms the “matrix” of clinical trials, and describes the extra income as a “big jump” financially above his pay at Wal-Mart. During his first year in our study, he had more difficulty qualifying for new studies, having screened for eight but only participating in three.

*Derek* is an African-American man in his 30's who has some college education and past employment in sales. He has remained unemployed since our first meeting at a clinic in the Midwest in 2013. When we met him, he was relatively new to phase 1 clinical trials (with only two completed) but participated in four additional studies within 1 year from enrollment in our study. Initially, he was exceptionally optimistic about the possibilities of making enough money in clinical trials to invest in new business ventures, such as purchasing the rights to a national franchise. More recently, however, he has acknowledged that he was somewhat overly optimistic about how much he could earn by participating in clinical trials, but he still has ambitions to be able to invest his earnings in a business. Meanwhile, he reports using clinical trial income to pay for household bills and living expenses.

*Martin* is a single man in his late 20's who identifies as more than one race. When we met him at a clinic in the Midwest, he was in the process of slowly completing his bachelor's degree while also doing phase 1 studies, which both helped with the bills but also created conflict with his class schedule. He reported participating in some 17 other clinical trials over the course of the 6 years he has done them and had traveled from coast to coast to enroll in studies. At present, he has graduated from college and identifies as self-employed as a research participant, screening for an additional 10 trials in the year since he was enrolled in our study. He is critical of the pharmaceutical industry but also says that he feels little choice about the studies in which he participates, since the income is needed to pay his bills and to look after his grandmother.

*Steve* is a white man in his mid-40's who started participating in clinical trials in 1991. He did not finish high school, but he holds a GED. He identified as self-employed as a trial participant when we first interviewed him, but has since done some seasonal and temporary warehouse work due to a lull in available trials for which he could qualify. He screened for 11 and participated in 4 clinical trials during his first year in our study. In spite of the difficulty he has had with finding and getting in studies, he does not envision stopping his trial participation at any particular point but is concerned about what he will do when he hits the upper age limit of 55 for many trials. He describes using his trial income in part to support a child and partner overseas. He had moved to a city in the Midwest primarily because he likes the clinic there as well as the location's proximity to other clinics in the region. Since our original interview, he has moved to a different part of the United States where he anticipates that the studies are better and he can live in closer proximity to one of his children.

#### IV. RE-ORIENTING BIOETHICAL WORRIES ABOUT PHASE 1 HEALTHY VOLUNTEER RESEARCH

In this section, we re-view the bioethical worries about phase 1 healthy volunteer research through the lenses offered by our healthy volunteer informants and argue for a reorientation of the bioethical investigation into the ethical issues at stake in phase 1 healthy volunteer research. The experiences of phase 1 participants highlight structural and system-oriented concerns that are not readily captured by the conventional bioethical focus on discrete exchanges, behaviors, and events taking place in phase 1 healthy volunteer research. Bioethicists have been primarily concerned with payment amounts, whether to allow certain exploitative exchanges, and the effects compensation might have on participant compliance. Based on the experiences of phase 1 serial volunteers, who are the norm in healthy volunteer trials, we instead draw attention to background social context, unknown long-term health risks, structural incentives for problematic behavior, and participant powerlessness in setting the terms of their exchange with clinical trial sites.

##### From Undue Influence and Coercion to Structural Coercion and Serial Risk Assessment

Although it is tempting to view undue inducement at its extreme as coercive, bioethicists have remained firm that coercion requires a threat of harm and that “inducements are offers, not threats, and they expand people’s options” (Wilkinson and Moore 1997, 378). Yet, at the same time, a theme among our income-dependent serial volunteers was a lack of genuine alternatives to study participation. For example, at his initial interview, Steve revealed, “I don’t have any better options . . . I’d rather be doing something else that paid the same amount of money, but I don’t have a college degree, so there’s really nothing I can do that’s gonna make me \$200 a day” [baseline]. And about his earlier job experience going door-to-door selling quotes for windows and siding, Martin reported, “I only made like \$144 my whole time, and that just made me realize, man, I’m busting my butt here . . . Long story short, [they see me as] a black man in a rich white neighborhood and they either think I’m trying to rob ‘em or . . . who’s this guy, you know?” [baseline]. For Calvin who, like Steve, has been participating in clinical trials for a very long time, the lack of viable alternatives for earning a reasonable income generated a palpable sense of weariness. During his 1-year interview, he said, “I’m like, ‘You know what, man? I don’t even care any more because I don’t even want to be here [doing studies]. I’m like that guy at the party that just doesn’t want to be at the party, I guess” [1-year].

These participants’ autonomy is not threatened by “volunteering” for trials under a specific threat or duress, as would be the case in a dyadic coercive

exchange. Nor does the concept of undue influence, which we discuss in more detail below, appropriately capture the diminished freedom regarding phase 1 trial participation that these participants relay. How, then, should we account for this sense of diminished freedom to decline clinical trial participation that stems from a lack of viable alternative sources of income? Fisher (2013, 357) has proposed the concept of “structural coercion” to account for “the ways in which broader social, economic, and political contexts act upon individuals to compel them to enroll as subjects in clinical research.” By moving beyond a “dyadic conceptualization of the researcher-participant relationship” (Fisher, 2013, 357) in which a specific threat of harm may be leveraged to induce participation, Fisher argues that coercive influences may also take place against a backdrop of *structural* violence, or “material injury that results from differential access to capital and human services, such as housing, education and health care” (Fisher, 2013, 361).

Structural coercion, then, is a sociological concept that serves as a corrective to the individualistic orientation of the philosophical view of coercion by reaching beyond the interpersonal threat of harm occurring within a specific exchange, to considering the background context against which a decision to participate in clinical trials takes place. Losing one’s home or transportation or failing to provide adequately for one’s children are individual problems that become acts of structural violence when shaped by profound social inequalities that systematically disadvantage some groups over others in society. With these economic threats in play, phase 1 clinical trial participation becomes a “choice” that is difficult not to make, once the option is on the table. Under structural coercion, social circumstances create the impetus for clinical trial participation so that it is not the researchers as individuals (or even individual pharmaceutical companies) who act coercively; rather, it is the research enterprise positioned against a background of social inequalities. Unlike the dyadic notion of coercion, which insists on locating a threatening individual or institution and a forced actor, the locations of moral responsibility and harm are more diffuse under structural coercion. A lack of voluntariness may stem from structural inequalities that are apparent in factors like Steve’s lack of educational attainment, having quit high school to support economically his mother and younger brother, or Martin’s inability to earn a living wage as a minority in a white neighborhood.<sup>4</sup>

Importantly, the concept of structural coercion does not apply indiscriminately to all serial participants who are income dependent on phase 1 trials. Bree, who holds a college degree and reports earning a stable income in past jobs, may not seem structurally coerced in her choice of clinical trial participation. She has more options than many of the other participants in our study, and she actively chooses phase 1 participation over more traditional forms of work. In line with that observation, Bree reported during her first interview that her freedom was enhanced through trial participation,

“For me, it was the freedom of being able to travel. And-and just knowing that I could make this kind of money and not really do much of anything was like, ‘What?! And this has been around for years?’ It really opened up my eyes” [baseline].

The concept of structural coercion gives us helpful insight into the diminished sense of voluntariness in phase 1 trial participation that other ethics concepts wielded in this arena do not. As Calvin’s reflections imply, limited earnings and increasingly precarious employment found elsewhere (Kalleberg, 2013) are structural factors exacerbated by disadvantages he faces across race, class, and address. This sense of diminished voluntariness is not accounted for in the frame of any discrete offer-acceptance event, as has been the focus of bioethical debates about coercive exchanges; it is a result of participants’ broader social and economic disenfranchisement. Further, the diminished voluntariness that the concept of structural coercion targets is also not adequately accounted for by other notions important to informed consent such as “undue influence” which, as we shall discuss next, focuses instead on a disruption of appropriate decision-making.

Many U.S. IRBs have held down payments to healthy volunteers as part of their mandate to protect research subjects from being unduly influenced to participate in clinical trials. Yet, when asked for their thoughts on undue inducement, our participant informants were puzzled, and even suspicious, as to the reasoning behind this purported concern. They could see why study sponsors might want to hold down payments out of self-interest, but were not impressed by the argument that lower payments might protect subjects. During Steve’s and Calvin’s 1-year interviews, they each offered particularly cogent observations regarding what they do and do not “understand” about undue inducement. Steve offered,

I don’t understand. What is their fear of the subject not being able to refuse? Because of the high pay? . . . As long as the risk hasn’t changed, then why would it--, why would they care whether the pay is too high as far as the subject is concerned? Obviously, it’s, you know, as far as the-the sponsor is concerned, I mean, obviously they don’t want to throw money away. But as far as the subject is concerned, yeah, I mean if the risk hasn’t changed, then I don’t understand why they’d worry about the subjects getting paid too much. [1-year]

Here, we see Steve reflecting his confusion about how the subject could be protected by lowering payments when what is important from a subject’s perspective is the objective risk inherent in the trial. This focus on the actual risk of the trial rather than how subjects perceive risk is a theme of Calvin’s ruminations about undue inducement as well, though he is more blunt in his criticism of the industry’s interest in promoting the very idea of undue inducement:

I do understand that some people are desperate enough to do virtually anything. That still doesn’t . . . excuse the fact that these, uh, facilities are kind of making

an excuse if they're saying that's the reason why they lessen or don't increase the stipend. Because again if you're saying that the medication in and of itself is potentially risky or riskier than the norm, then what are you saying about it if you actually do run it [the clinical trial]? Again somebody's still going to take it, so just because you're paying them less, did it lessen the risk? [1-year]

Recognizing that financial desperation may underlie participation in clinical trials, Calvin, like Steve, fails to see that as a reason to lower payments, since low payments will only serve industry interests and will not change the objective risk faced by participants.

Yet, while these participants remain nonplussed by the idea of undue inducement as providing a reason to lower payments, their reflections on their own trial participation makes clear that they decide about participation in trials depending on both the amount of compensation offered and their own personal circumstances. Bree, for example, reflects on her changing reasoning about whether to do HIV studies,

It was just always like, "HIV study, no-no-no-no." And then I had a friend who was like, "Eh, it's not so bad." And then I thought about it, I said, "Okay, maybe." But then things started to dry up [in terms of study availability], and then I thought, "Hmm, maybe it's time to reconsider." So I did do an HIV study. [baseline]

At the same time, Bree reports that she draws a line at participating in certain kinds of studies, "There's certain studies I don't touch, and even now I still won't touch them. I won't do spinal taps . . . I don't care how much money [it is], I just, I won't do it" [baseline]. Similarly, Martin reports that some studies are "off limits" for him. For example, he reflects on what he thinks is others' willingness to participate in the NASA bed rest study<sup>5</sup> saying, "When it's stuff like, yeah, you're gonna be on the bed for like 70-something days, now that's crazy . . . A lot of people will do it just because of the money. I'm not like that, you know" [1-year]. Although Martin reports not being "like" those who will agree to participate in an extreme bed rest study, he also recognizes that he participates over his own objection in studies that involve high numbers of blood draws: "When you're getting blood draws and one day you might have 19–20 blood draws, now that makes me, whew, I don't wanna do this, you know? . . . But you just looking at the money, so you gotta do it" [baseline].

From these passages we can see that Bree and Martin are more hesitant about some types of trials than others, but they will still participate in these when the money is right and they lack the option of alternative studies. Yet, each has indicated that there are some studies they would refuse to do regardless of compensation. What is unclear is whether certain circumstances might push them toward participation despite these personal preferences. In Steve's reflections on his past trial participation, we see quite clearly both his shifting willingness to participate depending on financial need and also a recognition that a certain level of "desperation" will prompt



participation even in some sense against his better judgment. He reported during his initial interview that, “There’s been a few times, you know, if the informed consent looked a little too scary, I’ll pass on it, you know, unless I’m really desperate” [baseline]. And he later said, “I used to have a policy of not even bothering to screen if it was anything under \$3,000. And now this past year, I’ve had to do that” [6-month].

The discussion so far suggests that efforts to avoid undue inducement by lowering payments to subjects may be misguided when framed as protection for subjects because what really matters to subjects is the background level of risk in a study. Lowering payments might not be an effective solution to participants’ consent to studies that they in some sense prefer not to do since fluctuating individual need and study availability may be more influential on their choices whether or not to participate. However, neither of these observations is novel in the debates over undue influence. Commentators on undue influence have argued that levels of financial compensation should not be held down when trial risks are no more than minimal (Dunn and Gordan, 2005; Phillips, 2011), and IRBs and bioethicists have long recognized that holding down payments is an anemic solution to the influences of precarious and divergent background financial need (see e.g. Macklin, 1981; Zink, 2001). Yet, some have also acutely felt the perversity of holding down payments only for some individuals who are worse off and so more likely to participate over their own objections (Macklin, 1981). Most importantly, perhaps, although the participant perspectives discussed here clearly show induced participation in trials that they in some sense prefer not to do, nothing about these participants’ decisions appear to reflect an *irrational* assessment of risk under the influence of a high level of compensation. What is reflected instead is a shifting willingness to accept certain kinds of risk, discomfort, or inconvenience, depending on a combined assessment of personal need and potential for financial benefit.

Yet, if the purported problem of “undue influence” to be avoided is compromised decision-making, particularly regarding risks and potential for benefit, then for serial participants we must look not only to individual instances of decision-making about participation, but also to decisional problems that arise in the longer term risk-benefit assessment of trial participation. Phase 1 trial consent processes currently are focused only on the risks presented by each individual study. The reality of serial participation is that the risks that are important to understand also include interactions between, and cumulative and longer term effects of, multiple investigational drugs.

Revising consent processes in ways that reflect the interests of serial trial participants could improve appropriate decision-making around risks of repeat volunteering. For example, there are often stated prohibitions about recent antibiotic use or repeated participation in studies with the same investigational drug. These prohibitions address known risks to serial participants, but the information is typically presented just as inclusion–exclusion criteria

for which participants are supposed to provide their trial or medical history to screeners. In this context, participants have an incentive to withhold details about their previous studies in order to qualify for the next one. If this inclusion–exclusion information were shifted to become risk information, underscoring that these criteria are for healthy volunteers’ safety rather than seemingly arbitrary details of the study protocol, serial participants would be in the position to make a more informed decision about protecting themselves from the potential cumulative risks of participating in phase 1 trials. In other words, serial participants currently lack contextualized information about how their enrollment in one trial might affect the risks of another. When risks are not limited to a discrete trial, investigators—who are well aware of healthy volunteers’ behaviors (Fisher, 2015a)—could better support healthy volunteers’ adequate assessment of trial risk by acknowledging serial participation.

The concerns raised by our participant informants reflect the need for informed consent processes that take serial participation into account. However, they also worry about cumulative effects of trial participation that they can neither anticipate nor adequately assess. Martin, Steve, and Derek each offer, in different ways, reflections that track the concerns that arise from longer-term phase 1 trial participation:

I’m very healthy and, you know, doing these can mess up your health . . . it might have happened something to me that I don’t even know about with all these investigational drugs. And people going to these things and mix up these drugs and don’t know what the, you know, repercussions might be. [Martin, 6-month]

I have worried a little bit that my fatigue and energy issues this past year--, it crosses my mind that, hey, it might have had something to do with all these [investigational] drugs I’ve been taking. [Steve, 6-month].

Certain stuff [physiological changes], you know, you might not pay attention to or feel at first, but let’s say, what if something don’t go back quite [to normal] within a month’s time, and I screen for another study, and they say, “Oh, you’re--you’re within guidelines of doing a study,” but I’m not in perfect health, you know, and I do things, do--do a medication that affects the same thing again, you know. [Derek, 1-year].

These participants are each concerned about the long-term effects of serial participation on their health. Yet, in the absence of better health risk information, and given the difficulty of determining whether or when health problems may be the result of their serial participation, the short-term *economic* risks associated with daily life encourage them to continue participating in spite of the potential health damage they fear they might be causing. In other words, the difficulty of assessing the health risks of *serial* participation potentially leads to precisely the kind of “under-estimation of risks and . . . over-estimation of benefit” (Philips, 2011, 213) that is an important focus of undue inducement. However, in this case, it is not any specific offer of

money that is problematic. The problem instead is the difficulty of assessing longer-term health risk within a set of practices designed to support risk-benefit appraisal on a study-by-study basis and where the uncertain and ambiguous long-term health impact is over-shadowed by the immediate financial benefit of participation.<sup>6</sup>

By shifting our attention to the health risks of *serial* participation, both known and unknown, we can acknowledge that concern over individual instances of irrational decision-making due to high levels of compensation draws attention to the wrong decisional problem for serial participants. Serial participants are neither hampered in giving informed consent to individual studies because of the undue influence of financial compensation nor are they simply savvy volunteers appropriately influenced by offers of payment for study participation. Instead, they are engaged in a practice of serial participation that, on one hand, is problematically ignored by the consent processes for individual studies and, on the other, undermines their very ability to adequately assess their own long-term health risks.

#### Exploitation and Justice: From Mutually Advantageous Consensual Exploitation to Social Justice and Routine Powerlessness

In the international context, use of placebo and lack of post-trial provisions have been a focus of concern for biomedical research in resource-poor countries (World Medical Association, 1964; Sofaer and Strech, 2011) and are generally cited as examples where exploitation may take place (Ballantyne, 2008; Snyder, 2012). In the US context, regulatory focus has been on meeting the moral requirements of justice through care in the selection of subjects (National Commission, 1979). However, concerns over the potential exploitation of research subjects through unfairly low payments for research participation in the United States and other resource-rich nations have been a subject of growing attention within bioethics (Ashcroft, 2001; Beauchamp, Jennings, Kinney, and Levine, 2002; Shamoo and Resnik, 2006; Phillips, 2011). Framed as a tension between a threat to voluntariness from high payments (through undue inducement) and to justice through unfairly low payments (through exploitation), a highly salient question arises as to whether there ought to be interference in mutually advantageous and consensual exploitation (MACE)<sup>7</sup> within phase 1 healthy volunteer research.

As we discuss next, our participant informant perspectives on payment rates do seem congruent with MACE. This in itself is an interesting finding, because it indicates that participants believe their compensation to be both unfairly low and also beneficial. Yet, we argue that more pressing problems for phase 1 serial participants are background social inequalities and routine powerlessness in setting the very terms of engagement in phase 1 healthy volunteer research, neither of which concern has been highlighted in the literature on phase 1 participation. Although both problems may be

analyzed relative to exploitation, as we discuss, we draw attention to these sources of concern as ethically significant independently of how exploitation is conceptualized.

When asked about payment rates for study participation, Martin straightforwardly accused pharmaceutical companies of “cheating” participants of what would be fair compensation for their role in the drug approval process: “They’re cheating us, these pharmaceutical companies are cheating us, and using us, and not paying us as much . . . ‘Cause without us, they don’t have a study” [6-month]. Other participants were more circumspect in their criticism, but drew particular attention to the fact that companies paid what they needed to in order to get studies done rather than what was commensurate compensation for the participant’s contribution to the process. Calvin asserted,

I mean, when you look at the big picture, this industry, the pharmaceutical industry is a multi-billion—with a B—dollar a year industry . . . And it is what it is, but it’s a hustle . . . [A decision is made that] this is how much out of the stipend we’re going to pay the volunteers, you know, and then many times it’s not, it’s less than what they could be paying the volunteers. [1-year]

Steve points out that the rate of compensation varies according to participant address as evidence that compensation rates are not based on a participant’s contribution:

I guess they pay as little as they think they can get away with. You know, unfortunately, there’s some facilities in more urban areas . . . where they pay ridiculously low, like \$60 a day . . . And yet, like the [study] I just did was paying \$400 a day. So I think they just try to, you know, they try to go by market forces and pay as little as they can get away with and still attract enough subjects. [1-year]

Although these comments do not show by themselves that payments to phase 1 research participants are exploitative, they do clearly highlight a perception that payments are incommensurate with appropriate compensation for participant contributions to the drug approval process. As unfair compensation is a hallmark of exploitation, the participants’ comments are in line with this concept. Also in line with the thinking of MACE, however, participants hold these views right alongside of views that payments are nevertheless advantageous for them even at their current level. Steve perhaps puts it best when he says,

Well, they do pay, they do pay just enough to make it worthwhile. In other words, they pay more than I’d ever make working a regular job for that same day’s work . . . I’m sure they could pay more if the--, but it would be a few less million going into the pockets of the investors. [baseline]

It would thus seem that exploitation in phase 1 trial participation, insofar as it occurs, is typically mutually advantageous and consensual, giving rise to well-known worries that limiting such exchanges is both harmful to, and

disrespectful of, the exploited parties by making them worse off and disregarding their free choices (Malmqvist, 2013).

Several commentators have offered criticism of the MACE framing of exploitation for its failure to address background injustices that form the context for exploitative exchanges (Snyder, 2012, Panitch, 2013, Malmqvist, 2013). An ongoing discussion centers on whether background social injustices ought to be included as part of a fuller account of exploitation (Snyder, 2012) or whether social injustice is a different moral problem from exploitation, but one that nonetheless offers a better account of why we ought to ethically reject, and even interfere with, some MACE exchanges (Malmqvist, 2013). From our perspective, in whatever way we delimit the concept of exploitation, MACE becomes a less significant frame for the justice issues arising in phase 1 healthy volunteer research than the more pressing upstream problem of what social arrangements create a fertile ground for the exploitation of certain groups and individuals. Highlighting specific examples of participants' pervasive lack of power in setting the very terms of their exchange with clinical trial sites, we draw attention away from discrete unfair financial arrangements to the structural conditions that create opportunities for exploitation.

Participants in phase 1 trials are *sometimes* middle- or upper-middle-class college students who want to make extra money to pay for a vacation (Tolich 2010), artists who prefer the episodic work of phase 1 trials to the grind of jobs that leave little time for their creative endeavors (Abadie 2010), or individuals who could pull in a reasonably high salary from "regular" employment but prefer the relative freedom of periodic income from trial participation (Bree from our sample is one such person). Much more frequently, however, phase 1 healthy volunteers are individuals with few options for earning a living wage due to low educational attainment, limited job skills, impoverished neighborhood settings, or even a history of incarceration (Cottingham and Fisher, 2016). They also tend to be older (30s or 40s) and continue to participate in phase 1 studies for years, although the frequency of their enrollment can vary (see Abadie, 2010; Fisher, 2015a). For example, Steve became a phase 1 trial participant against the backdrop of a changing economy in which niche retail stores (his former employers) became obsolete and with few other options, since he quit attending high school in order to help out a struggling mother and younger sibling. Given this context, *if* Steve's participation in a particular trial counts as mutually advantageous and consensual exploitation, questioning whether to interfere in or allow Steve's decision to participate seems an anemic response to addressing the potential injustice of his situation. Instead, focusing on the upstream social problems that create opportunities for downstream exploitative exchanges, along with the structural factors that allow researchers and pharmaceutical companies to take advantage of these social deficits, offers much richer entry points for concerns about justice (on both phase 1 and

later phase clinical trials, see [Corrigan, 2003](#); [Fisher, 2007, 2009](#); [Kingori, 2013](#)).

The exploited are typically not in a position to set the terms of an exchange. Rather, they are required to accept or reject terms set for them by others. One way that participant powerlessness surfaced in our discussions with phase 1 healthy volunteers was in the threat of being “banned” from certain study sites. Once banned, participants would not be able to earn an income at those study sites for an extended period ranging from months to life—sometimes these sites were those most conveniently located, or otherwise favored by, the particular participant. In theory, potential participants are banned for behaviors that put study validity or participant or staff safety at risk, such as not heeding 30-day washout periods between trials, testing positive for illicit drugs, causing disruptions during a trial, or not adhering to the diet or other restrictions during a trial. However, because there are no formal constraints on banning practices, participants can also be banned for having vitals or laboratory values that are out of range during screening visits or having experienced an adverse drug effect in a previous study. In other words, participants are banned for reasons that are both within and outside of their control.<sup>8</sup>

In practice, participants felt a generalized concern about being banned for reasons that were not transparent to them. In the following passage, Steve describes an exchange in which he found out he was banned from one site without warning or even an explanation of the reason for the ban:

They had a \$3,500 [Midwest clinic] about a month ago, and I called to screen for that. And the phone screener told me I was banned. I said, “Okay, why exactly am I banned?” She said, “For noncompliance,” and that’s all she knew . . . [A supervisor later] said that, “Well, when they say noncompliance, that’s just a generic term they use when they ban someone.” . . . I had no incidents there. No one—that was my first and only study at [clinic]—none, no one ever came to me and said, “You’re not being compliant,” or no one wrote me up for anything . . . I complained about a couple of things, and maybe they’re being petty and vindictive about that. You know, they don’t want anyone, you know, if someone complains, they--they, maybe they want to ban them for that . . . That cost me \$3,500, potential \$3,500, and, you know, I got these two kids I got to help support. [6-month].

In spite of his efforts, Steve could not get an answer from the clinic about why he had been banned. As such, it is impossible to know how the clinic came to its decision or whether it was justified. Some commentators might point out that if the clinic’s decision was justified based on rule-breaking behavior, Steve was not powerless in avoiding this consequence. While we agree that this could be the case, the lack of transparency in how decisions to ban participants are formulated or justified highlights participants’ experience of powerlessness in the face of trying to earn their income from trial participation. Unlike a regular job, where employees typically have to be



given a reason (whether it is palatable to them or not) for dismissal, phase 1 healthy volunteers are provided no such information and hence cannot contest an unjustified ban.

Even so, it could be pointed out that participants have no right to be selected for research and so banning practices also require no explanation or justification. However, the problem of participant powerlessness holds independently of whether they have a right to be included in clinical trials. Presumably, problematic exploitation can take place whether or not participants have such rights; similarly, pervasive powerlessness in setting the terms of their exchange with clinical trial sites, participants' source of livelihood, is problematic independently of a right to be included in trials.

In their vulnerability to the terms of exchange that others set, participants are left both without the power to make demands, but also with a generalized concern that behaviors that *are* absolutely within their "rights," but are not in the interests of the trial sites or pharmaceutical companies, may lead to negative consequences for them. In the example above, Steve raises this concern with respect to possible repercussions for complaints he made. Martin describes a concern along similar lines with regard to a core tenet of research ethics—the right to withdraw from a trial. He explains,

They saying you have the right to leave when you want, but you really don't. Like, 'cause sometime there they'll use that against you for something later, you know, they'll say, "Oh, you leaving a lot," or, "Oh, you don't make screenings, oh." You know what I mean? [1-year].

Other ways in which the lack of power to set the terms of exchange arise include participants being strung along with a promise of potential trial earnings but with no guarantee of acceptance into a trial. Since potential participants will often travel long distances for an opportunity to join a trial, they develop expertise in ascertaining the likelihood of getting into any given trial. However, even when a trial seems a sure thing, the power to accept or reject participants—or hold a trial at all—is held by study sites and pharmaceutical companies alone. Martin describes his reaction to an instance in which he traveled a long way for a trial but ended up not making the study:

I'm like, "Oh, look, I came from [1,400 miles away], you know. Ya'll need to get on these people that are over the phone and to tell us the truth [about our likelihood of getting selected]." Because they told me that I was basically in . . . And I kept asking them at the screening and everything. They were real tight about it. And my thing is, like, for people who are local, maybe you can do that. But for people who travel half of the United States, they need to let them people know . . . [This happened again in another study where] I had to rent a car like for \$90. Ended up, all the bills, I paid like \$102, just to get out there. [1-year]

Derek describes an instance in which he was not rejected for a phase 1 trial, but instead the trial was canceled altogether. Because potential participants

were informed late in the night before the scheduled screening day, he felt like he had been subjected to a “bait and switch” maneuver. He explains,

I went to go and screen . . . got there that night to the hotel, and they called me 9:00 at night to cancel the study. Yep . . . they called people late that night to tell them they canceled the study and people that came all that way, but they told me I could screen for another study that—following morning. And so I was like, “You know, I’ll at least find out [about it],” and the study was something that was ridiculous, like 100 blood draws over almost a month for like \$4,000 . . . Man, that’s—that’s really, really taking advantage and making you feel like they was just setting people up to get them there and then get them into a different study. [6-month].

These instances of being banned, strung along, or taken advantage of offer an alternative entry point to the problems of serial participation from that of exploitation resulting from a specific unfair exchange. In particular, the structure of phase 1 healthy volunteer research allows trial sites to manipulate participant powerlessness in setting the very terms of the exchange. One might see the shared moral problem in these examples as that of using others as “mere means” to one’s own ends—a way of explaining exploitation that has been widely acknowledged as an alternative to the focus on an unfair distribution of benefit (Wood, 1995; Carse and Little, 2008; Snyder, 2012).

Although there is debate over the exact way in which using others as mere means could underlie the moral problem of exploitation in a research context (Carse and Little, 2008; Hawkins and Emanuel, 2008; Snyder, 2012), one way of addressing the problem practically may be instituting the kinds of employment protections that workers commonly rely on to uphold their bargaining power. In other words, to dispense once and for all with the notion that phase 1 trial participation is not a form of employment. As Carl Elliott describes the problem,

[G]uinea pigs [phase 1 healthy volunteers] are paid to test drugs, but everyone pretends that guinea-pigging is not really a job. I.R.B.s allow sponsors to pay guinea pigs, but, consistent with F.D.A. guidelines, insist on their keeping the amount low. Sponsors refer to the money as “compensation” rather than as “wages,” but guinea pigs must pay taxes, and they are given no retirement benefits, disability insurance, workmen’s compensation, or overtime pay (Elliott, 2008, 40).

If phase 1 healthy volunteers are able to gain recognition as employees, they *may* also be able to leverage the kinds of bargaining power that normalized work relations offer while also gaining some long-term protections consistent with their long-term contributions to research (Elliott and Abadie, 2008). Although this change would not solve all the problems of participant powerlessness—just as employment protections do not do so in other job contexts—it would have the potential to create in-roads for phase 1 participants to contribute to setting the terms of exchange for their participation.<sup>9</sup>

The concept of a MACE exchange fits well with serial participant perspectives on pharmaceutical company practices in setting compensation for participation in phase 1 trials. Participants affirm both that they are benefited by the level of compensation they receive and also perceive that compensation as unfairly low. However, we have pointed out that the moral problem of whether to permit or allow such exchanges is a less pressing justice problem for participants than the social inequalities that set the stage for exploitation, as well as the routine powerlessness of phase 1 participants to set the terms of their exchange with trial sites. Implementing workable solutions to the broader social injustices that underlie potentially exploitative practices may feel like a Sisyphean task. However, the routine powerlessness participants face results in identifiable clinical trial site practices that are highly salient to serial volunteers, such as taking advantage, banning without explanation, and stringing along potential participants. Although we have indicated how these practices can be understood as exploitative according to some understandings of the concept, we have drawn attention to these issues of routine powerlessness as both unexplored in the bioethics literature and salient to participants independently of whether they are understood *as* exploitative. The lived experience of phase 1 participants appears to reinforce an argument for the institution of job normalization as a partial solution.

#### Study Validity: Subversive Behavior or Structural Incentives?

Observers have raised ethical worries about paid phase 1 healthy volunteer research by pointing to the potential for undue influence (threatening voluntariness) and exploitation (threatening justice through unfair exchange). By attending to the voices of our phase 1 participant informants, in the preceding two sections we have re-framed these concerns to take into account structural coercion, decisional problems for serial participants, deficits in social justice, and participant powerlessness in setting the terms of phase 1 trial engagement. In the moral logic of the US regulatory guidance for human subject research, the third “leg” of the ethical stool supporting human subject research (in addition to voluntariness and justice) is an adequate risk-benefit profile. The moral principle underlying this requirement is that of beneficence (National Commission, 1979). While, at face value, worries about data validity seem to be primarily of scientific concern, the moral requirement for an adequate risk-benefit profile for human subject research quickly pushes data validity concerns into ethical territory.

Do phase 1 participants engage in behaviors that may undermine the validity of trial data? The short answer seems clearly to be “yes.” Our participant informants relayed examples such as ignoring the 30-day washout period, failing to ingest study drugs, and taking unauthorized medications. Bree describes her failure to adhere to washout periods when she first started participating in clinical trials: “When I first got into it, I was literally just going

right after the other, one after the other. I never gave myself time [between studies]" [baseline]. Calvin explains how he was able to avoid ingesting study drugs while participating in a trial in which oral drug administration was not directly observed:

I'll be honest with you, I threw the stuff in the garbage . . . They filled the bottle, we had to come in there like every week or something . . . I was actually counting [the pills], I was reading the thing and throwing each pill in the garbage, and it was terrible, I know I'm bad for that. [baseline]

Martin explains how he plans to ignore the prohibitions on nontrial pharmaceuticals during his next study: "I love Zyrtec [cetirizine]. Yeah. And even though there's a next one, you know, I'm gonna have to bring some in. Because, you know, that's a game with us, we like to sneak" [1-year].

Seen from one point of view, these are all significant examples of the kind of "subversive subject" behavior about which commentators like [Dresser \(2013\)](#) are so concerned. Each of these behaviors has a real likelihood of undermining study data in ways that may skew the risk-benefit profile of the research. Moreover, the participants seem well aware that the behaviors are problematic, whether or not they have given significant thought to the problem of study validity per se. Yet, seen from another point of view, this subversive behavior is better understood against a backdrop of structural aspects of phase 1 healthy volunteer trials that, on one hand, reinforce and encourage such behaviors and, on the other, incur a quite different set of problems for trial data validity. Next, we give examples to explain these points.

We learned in his 1-year interview that Martin plans to sneak cetirizine (an allergy medication) into his next trial site for personal use during the trial. However, recalling his baseline interview for our study, we are able to provide some background to this "subversive behavior," namely, an allergic reaction that Martin suffered during a previous study. During that trial, Martin had broken out in hives in reaction to the study drug. As he recalls,

I tried to hide it [the reaction], you know, 'cause we get that, so we thinking about the money, you trying to hide . . . So I'm looking like, you know, my lip bumped up. And they like, "What the hell going on?" you know. And I couldn't hide it no more . . . So I just came out and they kicked me out and took me home and all that, and you know, I ended up being stuck with their medical bill. [baseline]

One obvious structural problem with phase 1 research, then, is unavoidable—the risk of side effects with long-term consequences, including a need for medications that are not compatible with future "healthy volunteer" study participation. Yet, other structural problems raised by Martin's story are avoidable. Martin tried to hide his allergic reaction because he knew that he could not continue to participate in the study given his response to the drug. Since payment for participation is meted out over the course of the trial, typically with a completion bonus at the end that may constitute a significant portion of the payment, participants are 'incentivized' to complete

the trial and, inadvertently, to hide side effects that may undermine that goal. Martin's attempt to hide serious side effects is worrisome from the point of view of study validity, since such effects are exactly what the study should measure, but also because of the potential confounding influence that his cetirizine consumption may have in future trials.<sup>10</sup>

The requirement of a 30-day washout period between trials aims to lower the likelihood of study drug effect interactions—potentially dangerous for participants as well as problematic for trial data. The structural problem with this requirement is that the piecemeal nature of trial participation incentivizes “jumping” from one trial to another as a way to maximize potential earnings. Further, despite much discussion about, and some movement toward, co-ordination across study sites to keep track of serial participants, the 30-day break between studies is loosely enforced and largely reliant on subject self-report.<sup>11</sup> As Steve explains, it is easy for healthy volunteers to organize their trial participation in ways that avoid detection of back-to-back participation. He comments about a particular site, “They're one of the ones that has this kind of tracker thing where they coordinate with all the other facilities that are in this network so that they can know if you've done a study at one of these other facilities in the network.” However, he continues, “But the thing is [Clinic A] and [Clinic B] aren't in that network, so you can do a [Clinic A], and then the next day hop into [Clinic C], and [Clinic C] won't know. They'll only know if you did one at one of the other ones that subscribes to this tracking service thing” [1-year].

In these examples, we see structural incentives in healthy volunteer studies as the backdrop against which “subversive subject” behavior may undermine phase 1 trial data validity. Shifting the frame in this way moves the emphasis in promoting data validity away from responding to the bad behavior of individuals and toward policy and other systematic reforms that may ameliorate problematic incentive structures in this type of research. For example, with respect to reporting side effects, we see that current policies effectively “punish” compliant subjects who report side effects by cutting their pay and potentially saddling them with medical costs. An alternative would be to treat and monitor subjects experiencing adverse reactions in the facility by paying them the full study compensation, even if they no longer receive a dosage and are effectively dropped from a study. Such a policy should persuade subjects to report honestly side effects instead of hiding them. Furthermore, by treating any adverse reactions directly, subjects would not be expected, or tempted, to cure themselves using other medications that could compromise study validity.

In addition to raising problematic incentive structures that may undermine data validity through influence on participant behavior, our phase 1 volunteer informants also worried about problems for data validity introduced by the profit incentives guiding the pharmaceutical industry and trial sites. Derek offers an example of the way in which industry incentives could also undermine study validity:

Sometimes with some sponsors, them trying to get drugs passed, they're trying to get it in the certain standards or something or tight regimen, I think. Because if you saying that you just letting anybody that's healthy check in and do this drug, then that's saying one thing, but if you let the healthiest of healthiest people that's got the perfect heart rate, you know, perfect lab work, you know, blood work and everything do it, you know, then that means that nine times out of ten their metabolism is a lot higher and they're going to get-, they would get the medication out of their system faster. [6-month]

Indeed, many of our participants have complained that they “fail” their screenings not because their laboratory results are out of range when it comes to their general health, but because they are not healthy enough to meet the stringent inclusion–exclusion criteria for specific phase 1 trials. Although there may be good scientific reasons for these criteria that pharmaceutical companies could articulate, they also manipulate the definition of “healthy” and “normal” and potentially raise concern about the safety profile of new drugs when they are used in the general population. Seen through this lens, Derek’s implied criticism of phase 1 trial validity is turned somewhat on its head. As he explains it, the subversive behavior could be seen to reside with the clinics or pharmaceutical studies sponsoring the clinical trials. Whether or not that is the case, such stringent definitions of health might also further incentivize healthy volunteers to take supplements in order to pass screenings and stay in clinical trials, because they have to “game” the system to qualify for new studies. For example, Steve explained,

I think white blood cell count has been my main bugaboo over the years; that’s usually the reason I don’t get picked, is my white blood cell count is too low . . . the clinics always tell you they don’t know what, they just tell you it’s clinically insignificant, “It’s just outside of the parameters for our study.” And so I just, I just try and get, like there’s a supplement called Blood Builder that has iron and-and B vitamins in it . . . so I’ve been taking things like that on and off for years. [6-month]

Here, we see the clinical trial industry’s efforts to highly control the parameters of what counts as “healthy” perversely back-firing by creating an incentive for participants to take the kinds of supplements that could undermine data validity.

## V. CONCLUSION

The practice of paying healthy volunteers to participate in phase 1 research has engendered concern with respect to core moral tenets of human subject research: voluntariness, justice, and beneficence. Commentators have raised and rejected worries of widespread coercion and are divided over the nature and significance of any undue influence that payments may incur. Worries about exploitation of healthy volunteers have arisen in part as a counter-balance to tendencies to keep payments low in order to avoid undue influence.



Critiques highlight the balance of research harms and benefits in light of the subversive subject behaviors that are incentivized by such payments.

Typical bioethical worries about phase 1 trial participation tend to focus at the individual level and on particular exchanges. Examples include a focus on the potential for irrational responses to specific study offers as a way of understanding “undue influence”; an analysis of “coercion” as involving threat of harm or force by researchers against participants; the framing of exploitation as unfair financial arrangements between the parties to a transaction (allowing for the conundrum of whether to interfere in such exchanges that are also mutually advantageous and consensual); and attention to individual subversive behavior as potentially undermining study validity.

In this paper, we have complicated and shifted the framing of the bioethical worries raised about phase 1 healthy volunteer research by considering the perspectives of five phase 1 volunteers who are dependent on study income. We chose this approach because it helps to draw much needed attention to the practice of serial participation that is the norm in phase 1 clinical trials. We have argued that listening to phase 1 participants and attending to their background social contexts highlights structural and systemic concerns with phase 1 trials that are typically left out of the debates as currently framed. These include: the “choice” of trial participation often occurs against a backdrop of impoverished opportunity, the empirical reality is that evidence is lacking regarding the risks of serial study participation, unequal power relations in setting the terms of trial participation may be more problematic than unfair pay alone, and the structural features of phase 1 healthy volunteer research both incentivizes and allows “subversive” participant behavior.

We have thus made three specific contributions to the discussions over the ethics of phase 1 healthy volunteer research in light of serial participants’ experiences and perspectives. First, understanding structural factors that may diminish voluntary participation requires taking into account the background social context of healthy volunteers as well as the lack of basis for reasoned decision making regarding long-term serial phase 1 trial participation. Second, concerns over exploitation of healthy volunteers should move beyond questions of allowing or restricting mutually advantageous and consensual unfair exchanges to investigating the policies and practices that put healthy volunteers in a position of routine powerlessness to set the terms of their exchange with clinical trial sites. Third, attention to data validity problems that may undermine the balance of risk of harm and potential for benefit for phase 1 trials should shift to the incentives for rule-breaking that are both embedded in the way healthy volunteer participation is structured and in some cases to the advantage of trial sites and pharmaceutical companies.

In one sense, the experiences of serial phase 1 healthy volunteers reinforce common bioethical worries about payments for phase 1 participation. These

participants describe their transactions with clinical trial sites in ways that are consistent with the idea of MACE exchanges, frequently participate in trials in some sense over their own objections, and engage in behaviors that undermine the validity of trial data. In another sense, however, the experiences of serial participants advance insights into the ethics of phase 1 clinical trials far beyond these well-rehearsed concerns. Many of the problems facing serial participants have to do with entrenched social disadvantages that may keep them participating in phase 1 trials despite the potential health risks they face and their preference for other forms of work. With limited economic alternatives, these background social factors make participants vulnerable and powerless in the face of clinical trial site practices of banning individuals, pulling trials without warning, and offering less attractive trials as a substitute.

While we think moral attention should turn to systemic social issues undergirding the ethics of phase 1 healthy volunteer research, nearer range policy solutions can also encourage structural reform. Possible policy reforms include: transparency about why clinics ban individuals and limitations on appropriate banning practices; modifying payment structures to incentivize the reporting of side effects; assessing and communicating the risk factors relevant to serial participants; and extending worker-like protections to phase 1 participants. The perspectives and experiences of serial healthy volunteers illuminate the ethics of phase 1 practices beyond the current bioethical focus on discrete exchanges, behaviors, and events. Combined, bioethical and participant perspectives can more rigorously address the ethics of healthy volunteer clinical trials.

## NOTES

1. Not everyone has agreed to this view. For example, Ruth Macklin (1989, 1981) stated in early concerns about payment for research participation that the practice may be coercive and Joel Feinberg (1986) has argued that offers may coerce in some circumstances. However, the insistence that the term “coercion” not be applied to offers is about as settled a perspective as is possible within bioethics.

2. At the time of this writing, we had also conducted interviews two years from enrollment, but those interviews had not yet been transcribed or analyzed. As this article goes to press, all data collection for the project has been completed.

3. All participant names are pseudonyms.

4. Our aim here is not to argue generally for the relative merits of the concept of structural coercion over the standard bioethical notion of coercion in the phase 1 context. To do that, we would have to deal with pressing worries such as whether a felt (or even objective) lack of *freedom* to turn down clinical trial participation undermines informed consent as opposed to a challenge to *autonomous* consent (Wilkinson and Moore, 1997). We would also have to unpack further the question of whether a “genuine” offer can ever be coercive and consider arguments purporting to deny the relevance of background socioeconomic vulnerability in questions of coercion (Wertheimer, 2011). Finally, we would have to address the moral valence of such a concept, given the diffuse responsibilities and harms associated with it.

5. Participants often discuss the NASA bed rest study when talking about the limits to their participation in clinical trials. It has morphed into one of the urban legends that circulate among healthy volunteers about phase 1 trials (Fisher, 2015b).

6. It is important in this context that there are currently no objective data about the longer-term health risks of serial participation. It might be objected that serial participants are in no worse shape in this regard than one-time participants in phase 1 trials in which risks are also unknown at the time of testing. However, because they undertake multiple studies, serial participants are subject not only to quantitatively more risk of unknown side effects over time, but also to additional types of both predictable and unpredictable risk stemming from the interactive effects of their participation. Further, serial participants are not in a position to know definitely *whether* any particular latent health problem is traceable to their serial participation, so their uncertainty about the impact of participation may remain, even when a health problem is realized.

7. This concept is detailed in Alan Wertheimer's (1999) influential book on *Exploitation*, but has become widely discussed, sometimes with use of this acronym, including by Wertheimer.

8. We have also confirmed these banning practices with phase 1 clinics, which have different policies in place about what warrants placing someone on what they often call a "do-not-use list," but there is nothing in the scholarly literature we could find about this practice.

9. A somewhat contrary way of addressing the problem of taking advantage of phase 1 healthy volunteers' vulnerability would be to more fully recognize that phase 1 research ought to be guided by a norm other than the market logic that "agents should aim to negotiate the highest yield for themselves" (Carse and Little, 2008, 16). Such a norm may be inappropriate, for example, when other relational ideals are at play. Typical examples would be those of fiduciary, filial, or parental duty in which an obligation to further the yield for others, rather than for oneself, may be salient. For example, if researchers have fiduciary obligations toward healthy volunteers that transcend the economic goals of the pharmaceutical companies, such obligations could offer grounds for criticizing a market logic approach to compensation for phase 1 participants. A somewhat different line of criticism against a market logic approach would get traction if the exchange that takes place between pharmaceutical companies and healthy volunteers is a morally problematic form of commodification of the body. In that case, it is exactly the wrong moral solution to such exploitation to institute a formally recognized work relationship. Although we find both these lines of argument appealing, they are somewhat outside the scope of this paper and so we don't pursue them in this context.

10. Martin's story also reminds us of the endemic problem of failure to compensate injured trial participants (or even pay for their incurred medical care), but that is a separate moral problem from the issue of study validity.

11. There are now two commercial participant databases (i.e., Verified Clinical Trials and ClinicalRSVP) that sell their services to research clinics. As of this writing, less than half of US phase 1 clinics subscribed to either, so there is little mechanism to track healthy volunteers' participation.

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