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Response

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Bioethicists and others have long worried about distorted judgment resulting from financial desperation and exploitation of healthy participants in clinical research.^{1–3} In previous essays, Carl Elliott describes phase 1 research volunteers as desperate, marginalized and exploited members of society who often recklessly enroll in risky research because of the offer of money that is otherwise hard to come by and few other options.¹ Qualitative sociological and anthropological studies have also chronicled the circumstances and experiences of individual phase 1 volunteers and painted a picture of destitution and despair.^{1–3}

But do these qualitative descriptions tell a complete or accurate story? Recognizing a dearth of data on who volunteers for phase 1 drug development research, we describe sociodemographic characteristics of more than 1000 healthy phase 1 volunteers in Pfizer trials in three countries. Elliott notes that our data offer little reassurance against concerns about desperation and exploitation. Indeed, we found that half of our cohort of volunteers in phase 1 studies are low income, more than a third are uninsured, and many are unemployed—as he notes, only 12.8% of the participants in New Haven report full-time employment. On the other hand, our data show that although half of the cohort report household incomes of less than \$25,000(USA), the other half report incomes greater than \$25,000, and a small number even more than \$100,000. The vast majority (89%) told us that they felt no pressure of any kind to join the phase 1 study, and only 4.6% reported that they felt any pressure to join from their financial circumstances. Half of the overall cohort are employed full or part time, and an additional 13% said they were students. Two thirds have attended college. Finally, many of our respondents said they preferred research participation to other “jobs” because it gave them more time to do other things. These characteristics and responses diverge from those that suggest destitution and vulnerability.

Notably, respondents (up to 50% in some cases) also told us that they were definitely not willing to join some types of studies or accept certain side effects or study procedures even for money. There are likely some research volunteers among this cohort who are desperate, lack good judgement, and are willing to accept bad deals. Yet, there appear to be many others who weigh the choices they have before them for making money and decide that research participation under certain conditions is an acceptable –maybe even a desirable– option for them. In addition to the amount of money, most respondents (+/– 80%) ranked risks, staff competence and friendliness, contributing to medical research and helping future

patients as factors important to their enrollment decisions and this did not vary by income, employment, or previous research experience.

An important part of the dominant narrative about healthy participants in phase 1 research is that they are being exploited. Roberto Abadie writes “...even if subjects are aware of the risks they face and even if their rights are assured, are they not being exploited anyway as the weak link in the trial economy?” (2, p.3). Some regard healthy volunteer participation in research as exploitative because individuals accept risk with little or no potential for health related benefit- either as part of the study itself or from the knowledge and products ultimately produced. According to my friend Alan Wertheimer, wrongful exploitation occurs when one takes unfair advantage of another in a transaction- and often entails accepting uncompensated or inadequately compensated risk for the benefit of others.⁴ One possible way to minimize exploitation in this context, therefore, would be to increase benefits for participants- perhaps in the form of more money for time, better working conditions, remedies for research-related injuries- as Elliott himself has argued- and access to health insurance. Another approach is to keep risks low and ensure that rigorous monitoring and response plans are in place. Despite several well-known examples of healthy volunteers suffering serious risks, aggregate data suggest that the overall risk of serious adverse events in phase 1 research is actually quite low.⁵ Phase 1 volunteers certainly accept some risk, however, and the risks are uncertain. In addition, participants assume sometimes considerable inconvenience and discomfort in time, confinement, restrictions in diet and liberty, provision of blood and other body fluid samples, scans and other tests, and more. One aim of our studies was to better understand how phase 1 volunteers evaluate risks and inconveniences of research participation and whether there are boundaries around what they are willing to do. Our data suggest that healthy volunteers are willing to take on many diverse inconveniences and possible risks in research if the money is right; but the data also show that most make distinctions between studies and that their willingness to participate varies by type of studies, and by certain types of procedures and potential side effects. These choices may indeed be influenced by contemporary legends that phase 1 volunteers frequently recount and that “...establish a fictionalized gradient of risk in medical research...”³ However, reported willingness seems to also follow commonsense gradients of perceived risk, invasiveness, and reversibility. While Elliott says it is not surprising that people are reluctant to enroll in studies that they believe might injure them, “...even desperately poor people”, it is reassuring that participants’ willingness to enroll in studies does not appear to be driven by desperation and that the choices they make are reasonable.

Finally, Elliott describes unfortunate examples of pharmaceutical phase 1 research with the homeless and with undocumented immigrants. Without more light shown on phase 1 drug development research, we don’t really know how unusual or common these practices are. Phase 1 studies with healthy volunteers are an important part of the trajectory of developing safe and effective drugs, biologics, and devices to prevent or treat illnesses that plague many of us. Quantifying the number of institutions or centers that conduct phase 1 studies with healthy volunteers and thus the number of healthy volunteers in any given year is difficult. Yet, available information about contract research organizations (CROs), pharmaceutical Clinical Research Units, and academic medical centers suggests there are probably hundreds of distinct U.S. sites that conduct phase 1 trials and thousands of healthy participants.⁶⁻⁸

Assuring quality and minimizing possible exploitation will be facilitated by more data from these centers and from the phase 1 participants in their studies, by registries of participants,⁹ and through other ways to transparently share information.

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