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A National Registry for Healthy Volunteers in Phase 1 Clinical Trials

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Each year, thousands of individuals in the United States enroll in phase 1 drug trials as healthy volunteers to earn money. Payments for participation range from a few hundred to a few thousand dollars.¹ Some individuals have enrolled in as many as 80 phase 1 studies.² Professional research participants have developed their own social networks, Web pages, associations, and publications, which they use to learn about new studies, share information and experiences, and understand the ethical, regulatory, and scientific aspects of clinical research.¹ Some individuals pursue research participation as a full-time job and travel across the country enrolling in studies.¹ One person claims he earned \$32 000 in 2008.²

A significant risk of participating in a phase 1 drug trial is the possibility of a dangerous interaction between an investigational agent and another medication the participant is currently taking or has taken recently.³ This risk is especially great in phase 1 studies designed to induce toxicity to determine the maximum tolerable dose.³ Also, recent participation in another study can skew safety data. Most investigators minimize risks and reduce bias by excluding volunteers from phase 1 drug studies who have recently participated in another phase 1 trial. In the United States, the standard interval is 30 days.³ Although most drugs are eliminated from the body sooner than this, the 30-day interval is a standard safety measure, because some individuals may metabolize or eliminate drugs more slowly than others. Ideally, the protocol should specify an appropriate waiting period based on the half-life of the test agent, because in some cases, the interval may need to be longer than 30 days.

Although a waiting period for participation in phase 1 studies is necessary to ensure participant safety and data integrity, professional volunteers have a strong financial incentive to conceal recent or even current enrollment in phase 1 studies. One volunteer admitted that he often flouts the 30-day rule.² While the incidence of adverse drug reactions from overlapping trial enrollment is presumed to be rare, it may be underreported because participants who experience adverse drug reactions might not inform investigators making adverse event reports, to avoid jeopardizing their current or future enrollments.¹

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Because professional research participants may not disclose their enrollment in recent phase 1 studies, the United States should consider developing a national registry for healthy volunteers in such studies to protect participants from the risks of overlapping enrollment and to promote data integrity. Minimizing risks related to research participation is one of the fundamental ethical and legal requirements for research with human participants.⁴ All participants in phase 1 studies enrolling healthy volunteers deserve to be protected from the risks of overlapping enrollment, even those who make false statements about their prior study participation.

Several countries already have such registries. For example, France has had a national registry for healthy volunteers participating in clinical research studies since the early 1990s.⁵ In the United Kingdom, The Over Volunteering Prevention System (TOPS) database prevents healthy volunteers from participating too often in trials of new medicines.⁶ Research institutions in Canton Ticino, Switzerland, have also developed a registry for healthy volunteers to prevent individuals from enrolling in more than 1 study at a time.⁷

Registries also have been implemented in parts of the United States. In 2008, 5 research sites in South Florida developed a human participant registry to address the problem of overlapping enrollment in phase 1 studies. During the initial 18-week data collection period, 2081 individuals attempted to enroll in 27 phase 1 studies. Of these individuals, 50 (2.4%) attempted to enroll in another study within 30 days of receiving an investigational agent in a previous study, and 186 (8.9%) attempted to enroll within 60 days. Participants attempted to enroll within the 30-day period even though they were informed of the existence of the registry and the exclusion criteria.⁸ That a substantial percentage of individuals attempted to violate the 30-day waiting period suggests that overlapping enrollment in phase 1 studies is potentially a significant concern in the United States.

Although local registries can be implemented quickly, they can be circumvented because of geographic limitations. To adequately deal with the problem of overlapping enrollment, a national registry is needed. The registry should be linked to databases that provide investigators with important information related to the studies in which an individual has participated, such as interventions, drugs, estimated duration of the research, and contact information. Costs would be modest and could be financed by fees from study sponsors. Federal agencies that regulate or sponsor research with human participants, such as the US Food and Drug Administration (FDA) and National Institutes of Health (NIH), could make participation in the national registry a requirement for conducting a phase 1 trial enrolling healthy volunteers. The registry could be administered by the FDA or NIH.

Minimal identifying information would be required to prevent overlapping enrollment. The South Florida registry collects each study participant's initials and date of birth as well as the last 4 digits of his or her Social Security number and a fingerprint. The only information TOPS collects is a national insurance number for UK citizens or a passport number for noncitizens. A registry must use measures to protect confidentiality of the data, such as encryption, secure storage, and restricted access to prevent unauthorized use. If the registry contains no personal health information, it would not necessarily need to meet the privacy protections required by the Health Information Portability and Accountability Act, but it could be subject to the provisions of 21 CFR Part 11.⁹ Information about the registry would need to be included in protocols submitted to the study's institutional review board and in consent documents.

Some might argue that a research participant registry is not necessary because adequate safety measures are already in place to deal with the problem of overlapping enrollment.

However, data suggest that overlapping enrollment is a significant problem in phase 1 studies involving healthy volunteers,^{1,2} and it may become worse if the ranks of professional research participants increase. Others might argue that overlapping enrollment can be significantly reduced by taking away the financial incentive to cheat the system and not paying individuals for participating in these studies. However, it is unlikely that phase 1 studies enrolling healthy volunteers could achieve enrollment goals without offering participants a financial reward, because that is the main reason most individuals participate in such research.¹⁰ A national safety registry for study participants is a simple, straightforward way to minimize the risks and biases associated with overlapping enrollment in phase 1 studies and can be implemented at a low cost with minimal additional burden on investigators or sponsors.

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