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Healthy Volunteer Registries and Ethical Research Principles

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Abstract

The dual enrolling of phase i volunteers is a potential risk to subjects. it can also distort study results, threaten study validity, and possibly cause harm to future patients. existing subject registries differ in structure, funding, and governance. although the choice of the ideal system is driven by the scope of the risk and the funding mechanism, and is ultimately a value judgment of freedom versus paternalism, none of the registries significantly impinges on the tenets of ethically based research.

The Belmont report, issued in 1978 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, identified the key pillars of ethical research to be justice, autonomy, and beneficence. A key principle is that human-subject research has a responsibility to minimize harm and maximize benefit for participants as long as there is acceptable equipoise. There is, however, no absolute requirement of potential benefit of participation, even for those with disease. For example, although oncologists and patients participate in phase I oncology trials with a primary hope for therapeutic response, drug efficacy is not necessarily an immediate goal of these studies. The lack of understanding of this distinction by patients has been well described. Other study designs, such as those of noninferiority or comparative effectiveness, do not provide patients with a direct benefit of participation beyond access to care and/or financial compensation. Healthy-volunteer studies entail risk, with no potential for therapeutic benefit to participants. The lack of any potential health benefit outside of an evaluation of health status has often led to heightened institutional review board scrutiny for phase I studies. The focus of regulation in healthy-volunteer clinical trials is typically the short-term protection of subjects from harm directly related to study procedures. Outside of cumulative limits on radiation exposure, the role of the subject outside of an individual trial is generally not considered. The National Institutes of Health (NIH) and the US Food and Drug Administration (FDA) do not strictly limit the number of studies in which a volunteer can participate. It is merely suggested that subjects not enroll in consecutive studies without adequate time for washout of drug or intervention based on the biology of the system. However, there have recently been concerns about the potential for phase I volunteer participants to enroll in multiple clinical trials concurrently, with calls for a mandatory registry to track subjects.[1]

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Motivations for healthy-volunteer participants in clinical research can be altruistic, especially for disease-specific activists or those with afflicted family members. Generally, however, the prime motivation for most phase I trial enrollees who lack an underlying disease is in the financial compensation for participation.[2,3] Pursuit of compensation can incentivize subjects to enroll in multiple studies, despite the potential for personal injury, or risk of discovery and loss of access to participate at research sites. The ease of access to clinical research unit websites that list study calendars, as well as user-generated publications, allows subjects to remotely plan participation and allow overlap while minimizing study procedure conflict and detection by a clinical research site. Because of the ease of access, enrollment of individual subjects in more than one study simultaneously is problematic, not only for identification by the research sites but also for the safety of individual subjects. Multiple enrollment introduces occult bias, primarily through an increased incidence of adverse events and drug interactions that may alter pharmacokinetic or pharmacodynamic end points. These potential drug interactions also clearly increase the personal risk for healthy study subjects. The loss of study validity could be seen by subjects in a narrow sense as merely harming a commercial sponsor, without larger implications. However, aside from the personal risk taken by subjects via dual enrollment, the practice entails a potential to harm future patients. In the worst case, the unwarranted maligning of a drug because of an undisclosed drug interaction could delay the advancement of promising drug candidates or lead to restrictions on future use. Investigation of adverse events or unexpected results due to dual enrollment draws on investigator and sponsor resources and creates friction within the system that compromises the development of other drugs.

Countries have approached the problem of dual enrollment in a variety of ways (Table 1). Models have included mandatory government-run programs such as those in France and the southern Swiss Canton of Ticino, nonprofit voluntary systems such as the TOPS system in the United Kingdom, and a private-sector for-profit vendor in the United States and Canada. In a retrospective three-year study by clinical researchers in southern Switzerland, where a current register is in place, repeat volunteerism in their registered population ($N = 1436$) was only 0.2% (ref. 4). This regional registry mandates a minimum of a three-month drug-free interval. A German survey of healthy volunteers ($N = 440$) reported a dual-enrollment rate of ~3%. In a US survey of 60 subjects, 10% admitted to being dually enrolled in studies.[2] The most common motivation in all these reports was financial. By contrast, the North American registry provider Independent Data Integrator/clinicalRSVP reported a 12–18% rate of screening attempts before an appropriate washout period.

A potential argument against a central registry can be evaluated in terms of justice, subject autonomy, and cost. The primary potential harm to subjects is loss of privacy. For government-mandated programs in locales with centralized medical care delivery, the risk of data breach is not significantly greater than that associated with the standard delivery of medical care. In the UK and North American systems, which collect limited subject data, there is even less potential risk for confidential data release. Recent history of large-scale data breaches in various industries suggests that the potential for inadvertent release of clinical trial data from private and governmental databases is equally likely. The relative cost of administering a government-sponsored central registry can be viewed as an added cost to the clinical trial enterprise carried by society as a whole or, in a directed-funding model, by

the trial sponsors and research units. In the voluntary, private-service model, the cost is borne by the users of the system. However, as a primarily market-driven initiative, a registry's value for sites and sponsors can be based on a business calculus of the relative cost of ensuring patient safety and trustworthy data. In North America and the United Kingdom, subjects are free to limit their participation to research sites that do not participate in central registries. However, even in the mandatory systems of France and Ticino, the use of a centralized registry is not coercive and maintains subjects' autonomy. Although the use of registries that collect even limited information may dissuade subject participation in studies, the practice does not impinge on the ability of subjects to make informed decisions about participation. Indeed, the ability to volunteer in healthy-volunteer studies is not a right. By definition, potential subjects do not have a disease state for which treatment is needed.

The third Belmont principle is that of beneficence. Broadly stated, the questions are (i) whether there is a need to protect clinical trial subjects from themselves and (ii) whether a subjects' assertion that he or she is not dually enrolled is adequate to ensure their protection. The relative risks from loss of confidentiality are small, being equal to or less than those associated with routine medical care. The relative risks of dual enrolling to subjects are difficult to assess. Despite the catastrophic TeGenero incident in 2006, in which healthy volunteers suffered grave injury during a first-in-human investigation of the drug TGN1412, and a number of scattered individual events, participation in phase I clinical trials is, on the whole, not particularly dangerous.[5] Although there are limited central data to make quantitative assessments of risk, participation in phase I studies according to study protocol almost certainly poses less risk than many accepted sources of income in our society such as law enforcement, firefighting, and construction work. The poor evidentiary base of data makes it impossible to assess with precision the additional risk from dual enrollment. Accordingly, arriving at a dollar cost per event prevented via standard methods is not possible. Against this backdrop of uncertainty, however, it is in the interest of sponsors to conduct the best possible studies. Thus, sponsors have the fiduciary duty to ensure high-quality data and to make reasonable efforts to maximize the safety of subjects. Stakeholders in this process include not only sponsors but also contract research organizations and site investigators. Education of research subjects and systems to promote such education will clearly not prevent all dual enrollments but should be considered important elements of the informed-consent process.

The key question is whether the risk to subjects justifies the cost to the research enterprise (both private and public) of a mandatory registry. Notably, the need for a registry has not been identified by the US Department of Health and Human Services in the recently proposed overhaul of protection policies for human subjects. We argue that the evidence of risk to subjects from occult dual enrolling is not high enough in relation to cost and, to a lesser extent, potential loss of privacy to warrant a mandatory system. Although it has been proposed that the FDA or NIH could administer a mandatory registry, neither organization has expressed an interest in pursuing this. Establishing and maintaining a mandatory model would take resources, which in the current budgetary climate would involve moving funding from other core missions of these federal agencies. There is, however, no ethical conflict with the establishment of a voluntary system to prevent dual enrollment. A voluntary system is maximally efficient with dense adoption of a single registry, which should prevent dual

enrollers from seeking research units that lack registry verification. Such a registry system could lead to differential enrollment and adverse-event patterns at otherwise comparable sites. Non–sponsor-owned research sites that choose to voluntarily participate in a registry, without explicit sponsor assumption of costs, also put themselves at a competitive disadvantage when bidding for studies. In aggregate, however, a voluntary system has the benefit of spreading costs to the users of the system, as well as preserving the right of subjects to enroll at research sites not participating in the system. Modern evidence-based medicine and drug development are based on the use of high-quality data to make cost–benefit analysis. Although the lack of evidence of benefit of a phase I subject registry should not prevent the phase I trial community from acting, the uniform institution of a mandate for subject registries is not yet supported by the extant data.

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Table 1

Phase I registries of healthy subjects in various countries

Database	Who enrolls	Exclusion/washout period	Data collection	Strengths/benefits	Weaknesses/risks	Multisite viewing of information?	Cost	Regulator
Southern Switzerland Regional Registry	Healthy volunteers Site participation mandatory	PI dependent, at least 3 months	Volunteer code (initials + DOB + gender + nationality), CRU, study name, and date that subject is allowed to participate again in another trial Data purge after 5 years	Subjects caught are excluded from all future studies. Only those involved with study can access information; no other sites can do so. Subject identity protected on computer with no network access and alarm system.	Subject cannot refuse to be on registry.	No	Government financed by exam/approval fees (~500 Swiss Francs per study)	Swiss National Science Foundation
United Kingdom/TOPS	Healthy volunteers for phase I trials Site participation voluntary	Systemic drugs: 3 months minimum Cannot receive >10 mSv of radioactivity in any 12-mo period	Unique ID (national insurance number or UK citizens or passport number) at screening and the date of last dose of study drug Data purge after 2 years	De-identified data Site has flexibility with trials that have long follow-up (>4 weeks) Simple, Web-based interface	Usernames and password protected by authorized users Input errors require calls to other sites to clarify participation history.	Web-based and all authorized CRUs can share/view whether a subject has registered but cannot view the last dose day (must contact the CRU).	Registered nonprofit organization Free to sites	The individual site and TOPS administration
France	Subjects in whom research has no direct benefit Site participation mandatory	PI dependent	Code derived from subjects' names/DOB; start/end dates of study; end date of exclusion period; financial compensation	Data purge 1 year after the last date is entered	Based on annual salary ($4,000 annually) No protection against ID theft, privacy Subject must show proof of national health insurance	All authorized research centers have direct access.	Government public finance	Ministry of Health
United States and Canada/clinicalRSVP	Any subject who receives compensation for trial Site participation voluntary	PI/study dependent	Biometric data (fingerprint code), last dose date Data purge after 5 years	Subjects can dispute information entered into database if not accurate Transparent tracking and auditing Limited	Voluntary basis allows subjects to seek nonparticipating sites when dual enrolling. Effectiveness is reduced unless many sites in a region participate.	Sites can view only last date of study drug administration.	Private sector training + install = ~$ 1,500 $40 per subject per study	Private corporation

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Database	Who enrolls	Exclusion/washout period	Data collection	Strengths/benefits	Weaknesses/risks	Multisite viewing of information?	Cost	Regulator
				collection of subject data				
United States and Canada/Verified Clinical Trials	Any subject who receives compensation for trial Site participation voluntary	PI/study dependent	Web-based portal	Validity of subject identification checked against publicly available databases.	Voluntary basis allows subjects to seek nonparticipating sites when dual-enrolling. Effectiveness is reduced unless many sites in a region participate.	Sites can view whether a subject is eligible.	$500 per study	Private corporation

clinicalRSVP, Clinical Research Subject Verification Program; CRU, clinical research unit; DOB, date of birth; mSv, millisievert; PI, principal investigator; TOPS, The Over Volunteering Prevention System.

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