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Healthy Volunteer Registries and Ethical Research Principles

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Introduction

The dual-enrolling of phase 1 volunteers is a potential risk to subjects. It can also distort study results, threaten study validity, and may cause harm to future patients. Existing subject registries differ in structure, funding, and governance. While the choice of the ideal system is driven by the scope of the risk, funding mechanism, and is ultimately a value judgment of freedom vs. 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 key pillars of ethical research to be justice, autonomy and beneficence. A key principal 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 for participation for even those with disease. For example, while oncologists and patients participate in phase 1 oncology trials with a primary hope for therapeutic response, a primary goal of these studies is not necessarily drug efficacy. The lack of understanding of the distinction by patients is well described. Other study designs, such as those of non-inferiority or comparative effectiveness, do not provide patients with a direct benefit of participation, outside of 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 (IRB) scrutiny for phase 1 studies. The focus of regulation in healthy volunteer clinical trials is typically of 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 and Federal Drug Administration do not strictly limit the number of studies in which a volunteer can participate. It is suggested merely that subjects should not consecutively enroll in studies without adequate time for washout of drug or intervention based upon the biology of the system. Recent attention, however, has been raised about the potential of phase 1 volunteer participants to enroll in multiple concurrent clinical trials, with calls for a mandatory registry to track subjects.(1)

Motivations for healthy volunteer participants in clinical research can be altruistic, especially for disease-specific activists or those with afflicted family members. For the most part, however, the prime motivation for most phase 1 trial enrollees who lack of 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 web sites which list study calendars, and 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, enrolling in more than one study at a time is a problematic issue not only for the sites to identify but also for the safety of individual subjects. Multiple enrollment introduces occult bias, primarily by an increased incidence of adverse events and drug interactions which may alter pharmacokinetic or pharmacodynamic endpoints. 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 only harming a commercial sponsor without larger implications. However, outside of the personal risk subjects take on from dual enrolling, the practice entails potential to harm future patients. In the worst case, the unwarranted maligning of a drug due to an undisclosed drug interaction could delay the advancement of promising drug candidates, or place restrictions on future use. Investigating adverse events or unexpected results caused by dual enrolling utilizes investigator and sponsor resources and is a friction upon the system that detracts from the development of other drugs.

A number of countries have approached the problem of dual enrollment in a variety of ways. (Table) Models have included mandatory government-run programs, such as those in France, and the Southern Swiss Canton of Ticino, non-profit voluntary systems such as the TOPS system in the UK, and private sector for profit vendors in the United States and Canada. In a retrospective three-year study done by clinical researchers in Southern Switzerland, where

there is a current register in place, repeat volunteerism in their registered population (N=1436) was only 0.2%.⁽⁴⁾ This regional registry mandates a minimum of three-month drug-free interval. A German survey of healthy volunteers (N=440) reported dual enrollment rate of ~3%. In a US survey of 60 subjects, ten percent admitted to being dually enrolled in studies.⁽²⁾ The most common motivation in all these reports was financial. In contrast, the North American registry provider IDI/Clinical RSVP reports a 12-18% rate of screening attempts before an appropriate wash out period.

A potential argument against a central registry can be assessed in terms of justice, subject autonomy and cost. The primary potential harm to subjects is that of loss of privacy. For the governmentally mandated programs in locales with centralized medical care delivery, the risk of data breach is not significantly more than that associated with the standard delivery of medical care. The UK and North American systems, which collect limited subject data, have 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 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, the value of a registry

for sites and sponsors can be made on a business calculus of the relative cost of ensuring patient safety and trustworthy data. In North America and the UK, subjects are free to limit participation to research sites that do not participate in central registries. However, even in mandatory systems of France and Ticino, the use of a centralized registry is not coercive, and autonomy of subjects is maintained. While 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 principal is that of beneficence. Broadly stated, the questions are 1) is there a need to protect clinical trial subjects from themselves, and 2) is the subject's attestation that they were not dually enrolled adequate evidence to ensure their protection? The relative risks from loss of confidentiality are small, being equal or less to that 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 had grave injury during a first in human investigation of the drug TGN1412,, and a number of scattered individual events, on the whole participation in phase 1 clinical trials is not particularly dangerous.(5) While there are limited central data to make quantitative assessments of risk, participation in phase 1 studies according to study protocol almost certainly poses less risk than many accepted sources of

income in our society such as police, fire fighters, and construction workers. The poor evidentiary base of data makes an assessment of the additional risk from dual enrolling impossible to make with precision. Accordingly, using standard methods to place a dollar cost per event prevented is not possible. Against this backdrop of uncertainty however, it is in the interest of sponsors to conduct the best studies possible. This includes not only the fiduciary duty to ensure high quality data, but also in making reasonable efforts to maximize the safety of subjects. Stakeholders in this process include not only sponsors, but also contract research organizations and site investigators. Subject education and systems to promote it will clearly not prevent all dual enrollment, 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. Of note, the need for a registry has not been identified by the Department of Health and Human Services in the recently proposed overhaul of human subjects protection policies. 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. While 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 prevents dual enrollers seeking research units without registry verification. This could result in differential enrollment and adverse event patterns at otherwise comparable sites. Non-sponsor owned sites, which choose to voluntarily participate in a registry, without explicit sponsor assumption of costs, also put themselves at 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 participate at research sites not participating in the system. Modern evidence based medicine and drug development are based upon the use of high quality data to make cost benefit analysis. While the lack of evidence of benefit of a phase 1 subject registry should not prevent the phase 1 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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Conflict of Interest

The authors declare no conflicts of interest.

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Table: Phase 1 Registries

| Database | Who enrolls | Exclusion/ washout period | Data Collection | Strengths / Benefits | Weaknesses / Risks | Multi-Site 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), clinical research unit, study name, and date that subject's allowed to participate again in another trial Data purge after 5 yrs. | If subject caught, they are excluded from all future studies. Only those involved with study can access information; no other sites. Subject identity protected on computer with no network access and alarm system. | Subject cannot refuse to be on registry. | No | Government Financed by exam/appro val fees~500 Swiss Francs/stud y | Swiss National Science Foundation |
| United Kingdom/ TOPS | Healthy volunteers for Phase 1 trials. Site participation voluntary. | Systemic drugs - 3 months min; -cannot receive > 10 milli-Sv of radioactivity in any 12-mo pd | Unique ID (national insurance # or UK citizens or passport # at screening and the date of last dose of study drug Data purge after 2 yrs. | De-identified data. Site has flexibility with trials that have long follow up (>4wks). Simple, web- based interphase | 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 if a subject has registered but not the last dose day (they must call the CRU) | Registered non-profit organization Free to sites. | The individual site and TOPS Administ ration |
| France | Subjects in whom research has no direct benefit Site participation | PI dependent | Code derived from subject's names/DOB; start/end dates of study; end date of exclusion pd; \$ compensation | Data purge 1 year after the last date is entered. | Based on annual salary (\$4000 annually). No protection against ID theft, privacy. | All authorized research centers have direct access | Government Public finance | Ministry of Health |

| | | | | | | | | |
|-------------------------------------------|-------------------------------------------------------------------------------------|--------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|----------------------------------------------------------------------------------|---------------------|
| | mandatory | | | | Subject must show proof of national health insurance | | | |
| USA & Canada/ ClinicalRSVP | Any subject who receives compensation for trial Site participation voluntary | PI/study dependent | Biometric data (finger print code), last dose Data purge after 5 yrs. | Subjects can dispute information entered into database if not accurate. Transparent tracking and auditing Limited collection of subject data. | Voluntary basis allows subjects to seek non-participating sites when dual enrolling Effectiveness reduced unless many sites in a region participate | Sites can view only last date of study drug administration | Private Sector Training + install = ~\$1500 \$40 per subject/study | Private corporation |
| USA & 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 publically available databases | Voluntary basis allows subjects to seek non-participating sites when dual enrolling Effectiveness reduced unless many sites in a region participate | Sites can view if subject is eligible | \$500 per study | Private corporation |

PI = Principal Investigator; DOB = date of birth; TOPS = The Over volunteering Prevention System; CRU = clinical research unit.