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Policy recommendations for implementing registries to minimize over-volunteering in Phase I clinical trials

Authors:
Roberto Abadie, Ph. D. Department of Kinesiology, School of Education, University of Wisconsin-Madison, WI, USA

Jill Fisher, Ph. D. Center for Bioethics, Department of Social Medicine, School of Medicine, University of North Carolina at Chapel Hill, NC, USA.

Shadreck Mwale, Ph. D. Geller Institute for Aging and Memory, University of West London, UK

François Bompart, MD. INSERM Ethics Committee, Paris, France.

François Hirsch, Ph. D. INSERM Ethics Committee, Paris, France.

Corresponding author: Roberto Abadie, Ph. D. Department of Kinesiology, School of Education, 470 N Charter St. Madison, WI 53706. rabadie@wisc.edu

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Every year, thousands of Phase I interventional clinical trials are conducted globally, enrolling healthy human volunteers motivated primarily by financial gain[1-2]. To maximize payments—often in the thousands of dollars for a few weeks' trial—some volunteers participate in multiple studies simultaneously or without observing the required washout period between them—a well-documented phenomenon we refer to as "over-volunteering"[3]. By so doing, healthy volunteers may compromise their health and well-being. While serious adverse effects are rare, the experimental nature of Phase I trials, which for "first-in-human" studies are designed to trigger adverse events under controlled conditions[2], makes risks uncertain and unpredictable[4]—a concern that might be compounded by concealed trial participation, which may further increase the likelihood of adverse events.

Over-volunteering highlights important ethical issues. For example, in contexts like the US and other countries where there is no national healthcare system, the risk of injury to healthy volunteers is especially concerning and raises ethical questions about nonmaleficence and the oversight of clinical research. Further, the benefits and burdens of research are not fairly distributed; the disproportionate inclusion of economically disadvantaged participants, who are typically underemployed and undereducated, bearing risks to develop medications they might not be able to afford raises additional ethical concerns about justice.

Beyond the risks to healthy volunteers, another concern with over-volunteering is that it could undermine the internal validity of trial results. With over-volunteering, in particular, adverse events or other trial outcomes might be distorted by synergistic drug interactions with another clinical trial of which researchers might be unaware. While there are no publicly available data on the impact of over-volunteering on phase I trial results, responses from regulators and pharmaceutical actors suggest the problem is severe.

Therefore, participant registries designed to prevent—or minimize—over-volunteering in Phase I clinical trials should have an essential role in protecting healthy volunteers from risks while enhancing the validity of trial results. To be effective, registries should monitor trial participation comprehensively to detect all cases in which participants might enroll in more than one trial simultaneously or enroll in a trial without respecting the mandatory washout period[5].

That said, only a few countries have implemented registries to prevent over-volunteering in Phase I and other trials requiring healthy volunteers. In the 1990s, France was the first country to implement a centralized participant registry (called VRB, for Volontaires Recherche Médicale), which is managed by the French Health Ministry[6]. The French system requires investigators to consult the registry before including any healthy volunteer in a clinical trial. This ensures participants' compliance with any waiting period before taking part in another trial, and it also controls the amount of yearly compensation received by a single individual (currently a maximum of 6000 euros). In 2002, UK researchers established The Over-Volunteering Prevention System (TOPS), a free database that was initially used on a voluntary basis by clinical research centers and managed by an independent charity. In 2013, TOPS was transferred to the Health Research Authority within the National Health Service (NHS) and became a mandatory component of enrolling healthy volunteers in Phase I trials[7]. TOPS uses a green light system to indicate whether a participant has recently been enrolled in a trial in another research unit. Malaysia also has a registry system that is modeled on TOPS, and its development followed a similar trajectory from a voluntary to mandatory system. Specifically, the Malaysian Health Ministry became the registry's custodian in 2021 and required its use through the newly created National Healthy Research Volunteer Register (NHRVR).

Apart from national, country-level efforts to create and manage participant registries, several Contract Research Organizations (CROs) in India, the US, Germany, Belgium, and other countries have built their own voluntary registries to exchange information on healthy volunteers' trial enrollment among participating sites. For example, the private, regional, non-mandatory registry in India circumvents issues related to participants' lack of personal identity documents by relying on biometric information to prevent over-volunteering. A US-based company Verified Clinical Trials offers, at a fee, a verification system to detect the concurrent enrollment of research subjects. It also relies on biometric data to monitor compliance, but like other companies, does so throughout the life of the entire clinical trial and not just during intake[8]. Verified Clinical Trials currently operates in fifty-one countries in North America, Europe, and Asia, but it collects from and provides enrollment information only to the research clinics that are subscribers to the system.

As part of concerns about over-volunteering and other ethical issues that arise in healthy volunteer clinical trials, the international VolREthics (Volunteers in Research and Ethics) initiative, spearheaded by the French medical research agency's (INSERM) ethics committee, published a Global Charter for the Protection of Healthy Volunteers in Clinical Trials in April 2024[9]. The main objective of the VolREthics initiative, of which all the authors are a part, is to give voice to an important category of clinical research participants who are rarely identified as such in international guidelines and recommendations. In preparation for the Charter, an expert working group presented several tailored recommendations to encourage good practice in designing and implementing registries on a global scale. The Charter's Article 10 reads: "Countries should develop and maintain mandatory systems across all clinical research settings to prevent over-volunteering. Consistent with national and international data privacy

requirements, these systems should enable individual participant identification to ensure healthy volunteers adhere to the exclusion periods between trials. Wherever possible, these systems should operate across national borders".

Given the diversity in regulatory approaches, scientific and technological infrastructures, and national cultures, the Charter did not endorse a specific participant registry system. However, our group recommends that registry use should be made mandatory through regulations for all private and public institutions that conduct studies involving healthy volunteers. Registries should have at least a nationwide scope and ensure data confidentiality by restricting access only to authorized persons. In addition, access to registries should be streamlined and facilitated through integration with existing clinical trial platforms or research databases (e.g., ClinicalTrials.gov, Euclinicaltrials, WHO International Clinical Trials Registry Platform). Countries that wish to cap study participation, for example, by defining a maximum number of authorized trials or setting up maximum financial compensation amounts, as is done in France, could also implement such provisions.

CROs can play a critical role in volunteers' recruitment and are integral to effectively implementing any system to prevent over-volunteering. They should welcome a system that is simple to use and would enable them to quickly identify ineligible participants. Additionally, depending on how the system is set up, companies or researchers could, as a "side benefit," obtain early access to studies or exclusive recruitment opportunities through these registries.

For any participant registry, some key features should be considered to ensure the system's efficacy and confidentiality. All investigational units, whether public or private, should use a unique identifier for each participant to track their involvement across multiple trials and institutions. When countries have national identification numbers, these could be used; in

countries where this is not the case, registries could implement other options, such as biometric-based systems, as is currently implemented in India. The unique identifiers should be linked to participants' personal information while maintaining data privacy, allowing researchers to conduct real-time updates on any potential conflicts or safety concerns. Washout periods could either be indicated by investigators for each trial in which a volunteer participates (as in France) or be a national standard time period (as in Malaysia). Access to the registry should be limited to formally accredited persons. Data privacy should not only be ensured as part of basic respect for individuals, but it is also an important issue for healthy volunteers, who do not always inform families and relatives of their participation in clinical trials. In turn, regulators should standardize registry requirements, provide sustainable funding and resources for proper oversight of the registry's infrastructure, and conduct regular audits and inspections along with feedback mechanisms to gather input from researchers, trial sites, sponsors, and volunteers to improve register functionality. A final recommendation is to foster international collaboration by encouraging global registry adoption for wider impact and data sharing.

We recognize that while national or even supranational registries to prevent over-volunteering can play an important role in protecting healthy volunteers while enhancing data validity and trial integrity, important barriers to implementation remain, as exemplified by the dearth of existing national registries. The scientific, technical, and regulatory resources required to implement national registries might not be available or might be too costly or burdensome to implement, particularly in poor or even middle-income countries, impeding their widespread adoption. At the same time, while the pharmaceutical industry and CROs might welcome additional tools to prevent over-volunteering, mandatory compliance with registry requirements for privacy and confidentiality can produce unwanted delays in drug development and rising

operational costs. A priori, this barrier might be significant given that the pharmaceutical industry can already rely on private initiatives like Verified Clinical Trials to monitor concurrent enrollment should they choose to. Still, like in the Indian context, geographic limitations, financial costs, and the voluntary and subsequently incomplete adoption of the system conspire against its effectiveness[10]. Healthy volunteers learn which research clinics use these registries and circumvent the system by enrolling at nonparticipating sites[11] or, as in Europe, cross national borders to participate in trials in countries with no mandatory registry. One final barrier to implementation comes from healthy volunteers themselves. For those who enroll serially in Phase I trials, registries will effectively limit opportunities for financial gain, even if their intention is to reduce those participants' risk of harm from adverse events.

Collaboration and dissemination

To overcome barriers to implementation, registries will need the buy-in of diverse actors, from governments to CROs, pharmaceutical companies, and healthy volunteers. While our Global Charter for the Protection of Healthy Volunteers in Clinical Trials engaged with members from each of these stakeholder groups, dissemination efforts should be broadened to include the International Consortium for Innovation & Quality in Pharmaceutical Development and the International Council for Harmonization of Technical Requirements for Human Use, among others. Broad collaboration will be required to make strides in the implementation of registries to prevent over-volunteering.

As noted above, the VolREthics Initiative does not recommend a specific system, only broad guidelines to which any participant registry should adhere. Furthermore, we recognize the limitations of implementing global or even multinational registries but suggest that good

practices for setting up registries should aim for the broadest coverage possible[12]. After all, a registry's effectiveness is directly linked to its ability to monitor and prevent over-volunteering consistently and comprehensively. A patchy registry will be less likely to detect cases where healthy volunteers fail to adhere to the trial requirements. Broadly adopting registries will protect healthy volunteers from short- and, potentially, long-term risks[13] while also enhancing trial results' transparency, reliability, and validity, thereby contributing to developing safer and more effective drugs. Registries would also enable the collection of good-quality data on the numbers and types of clinical trials that involve healthy volunteers, therefore facilitating the development of better and more adapted protective measures to further protect this group and enhance their participation in biomedical research.

We declare no competing interests.

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