POLICY BRIEF

Healthy Volunteers in clinical research: making participation safe, fair and transparent

Key Messages

- Every year tens of thousands of healthy volunteers are involved in clinical trials in a wide variety of countries.
- In Low & Middle Income Countries, healthy volunteers are often disadvantaged individuals with low literacy levels who may be too poor to turn down the financial incentives offered.
- The emergence of the “professional volunteer” phenomenon - volunteers who repeatedly participate in clinical trials for financial gain - is a serious challenge.
- “Professional volunteers” may expose themselves to serious medical conditions and risk compromising the validity of the scientific results of the trials.

Recommendations

National Healthy Volunteer Registries can significantly reduce risks for healthy volunteers by monitoring repeated involvement of healthy volunteers in clinical trials.

A monitored cap scheme for financial incentives or a standardised compensation model for participation in clinical trials provides additional protection.

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Why it matters

Healthy volunteers are individuals with no known significant health problems who participate in research to test the safety and efficacy of a new drug, device, or intervention. Every year tens of thousands of healthy volunteers are involved in clinical trials in a wide variety of countries.

By being the first to test a new drug, device or intervention, healthy volunteers expose themselves to unknown risks or even possibly lethal harm. Despite this risk, ethical issues related to their participation in clinical research have not yet been adequately addressed. Neither the Declaration of Helsinki (2013) nor the Council for International Organizations of Medical Sciences guidelines (CIOMS, 2016) mention healthy volunteers.

Clinical trials and the enrolment of healthy volunteers in clinical research are essential to advancing medical knowledge and developing novel, lifesaving medications and treatments. The desire to help science, or others, is sometimes claimed as motivation for participation in these tests. However, in Low & Middle Income Countries (LMICs), the reasons for entering a clinical trial are undoubtedly linked to the offer of financial payment or the expectation of receiving some basic health care in return [Macklin, 2004; Grady, 2005; Ravinetto, 2015; Bompart, 2018].

In LMICs, healthy volunteers are often disadvantaged, vulnerable individuals with low literacy levels who may not fully understand the possible risks associated with their participation, or who may be too poor to turn down the financial incentives offered in exchange.

Vulnerability

"To be vulnerable means to face a significant probability of incurring an identifiable harm while substantially lacking ability and/or means to protect oneself".

Schroeder and Gefenas, 2009

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Healthy volunteers may be too poor to turn down financial incentives.

The Figures

As data on Phase I clinical trials are largely owned by pharmaceutical companies, numbers are difficult to verify. We are grateful to Sanofi for providing access to data, which combined with public databases[1] reveals that tens of thousands of healthy volunteers are recruited every year [Bompart, 2018]. The overwhelming majority of the studies they participate in are pharmacokinetic studies - performed to examine the absorption, distribution, metabolism, and excretion of an investigational drug or approved drug in healthy humans.

Table 1 Planned and ongoing Phase 1 studies reported in two Web-based databases September 2017

	TrialTrove database	Clinicaltrials.gov database
Africa	13	27
North America	310 (USA 289)	417
Central America	367 (Mexico 367)	4
South America	9	27
East Asia	388 (China 316)	150 (Republic of Korea 74)
South Asia	19	11
South East Asia	31	17
Eastern Europe	28	9
Western and Central Europe	216	284
Japan	22	15
Middle East	11	17
Pacific	49	40

Table 2 Sanofi-sponsored studies involving healthy volunteers 2014 - 2016

Total number of studies	Type and number of studies	Total number of healthy volunteers involved	Number of studies per country	
122	Pharmacokinetic studies (bioavailability, bioequivalence, drug-drug interaction): 113 "First-in-human" studies of New Chemical Entities (single or multiple ascending doses): 9	Approximately 4,800*	Canada Brazil Romania Czech Republic Germany USA/Canada France India Malaysia USA China Other	40 19 15 8 7 6 5 4 4 4 3 8

[1] The data is based on information retrieved from four sources: 1) Sitetrove, 2) the clinicaltrials.gov database from the US National Library of Medicine, 3) the Clinical Trials Registry of India and, 4) internal data from Sanofi, a global research-based pharmaceutical company.]

As compensation is always offered to healthy volunteers for involvement in a clinical study, economically disadvantaged individuals might feel compelled to enrol themselves or their children in a research study that they would not otherwise consider. The opportunity to earn money might overtake any concern about risks. Some turn their participation into a viable way of financially supporting themselves and / or their families and become "professional volunteers" [Tishler & Bartholomae, 2003; McHugh, 2007; Dresser, 2009].

"Professional volunteers"

Evidence of the "professional volunteer" phenomenon is well-documented [Grady, 2005]. "Professional volunteers" repeatedly participate in trials for financial gain. Findings from the US report cases in which healthy volunteers have enrolled in as many as 80 Phase 1 studies, sometimes travelling to different clinical sites within the country [Resnick & Koski, 2011]. The phenomenon highlights well known ethical issues pertaining to the globalization of clinical trials [Macklin, 2004; Ravinetto, 2015], such as undue inducement and the exploitation of vulnerable research participants.

Those volunteers who repeatedly participate in clinical trials may expose themselves to serious medical conditions, and also risk compromising the validity of the scientific results of the trials.

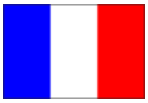
There is evidence that some professional volunteers surreptitiously [Dresser, 2013; Devine et al., 2015] enrol in more than one study simultaneously in pursuit of fees. In doing so, they may be tempted not to respect the mandatory waiting period, or 'wash-out' time, necessary for the body to eliminate the trial drugs before participating in a new trial. Additionally, in order to maximise earnings, they may not provide accurate information about their medical history, habits and adherence to the study protocol. Through repeated participation, such volunteers may experience unknown and potentially harmful drug-to-drug interactions. There is also a significant risk that they may harm not just themselves, but future patients too, by compromising and biasing the results of the trials.

Way Forward - National Healthy Volunteer Registries

The research community has voiced its concern about the safety and ethical issues of healthy volunteers' participation in clinical trials [Dresser, 2009; Habets et al., 2017; Bompart, 2018]. There is an urgent need to acknowledge the vulnerability of this group of research participants and take action.

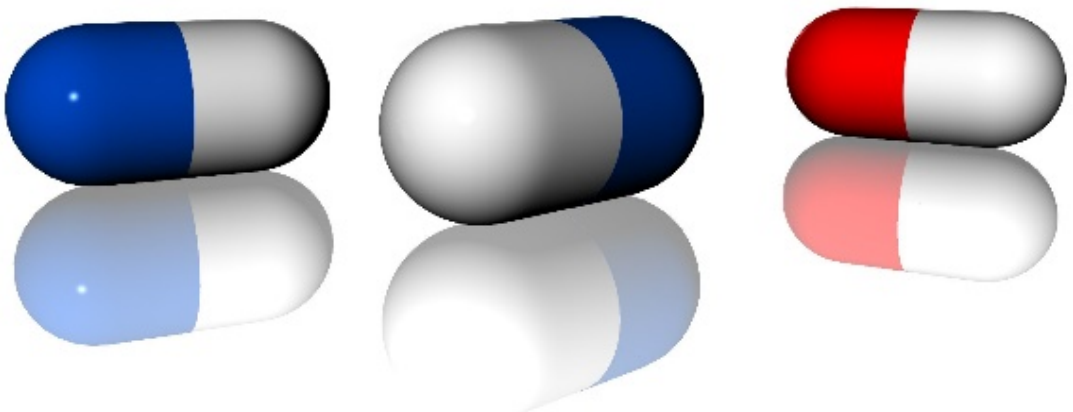
> Setting up National Healthy Volunteer Registries combined with monetary cap schemes provides urgently needed protection to healthy volunteers.

To date, France and the UK are the only countries where national registries have been set up.



The French national registry, the ***Volontaires Recherche Biomédicale***, is administered by the Ministry of Health based on a law ("*loi Huriet-Serusclat*") passed in late 1988, which established a legal framework for trials involving healthy volunteers. In France, healthy volunteers must be covered by the national "*Sécurité Sociale*" scheme and they must be registered in order to participate in any clinical trial. The information entered into the database includes the identity, date and place of birth of the volunteer, the dates of study participation, the amount of financial compensation received and, if appropriate, the post-study exclusion period during which no other study participation is allowed.

The UK national registry, the **Over-Volunteering Prevention System** "TOPS", was initially operated on a voluntary basis and administered by an independent charity following a study by the London-based Hammersmith Medical Research Phase I unit [Boyce et al., 2003]. The same unit has documented how joining the TOPS initiative has resulted in a decreasing number of research participants attempting to volunteer for UK Phase I trials within 3 months of completing another trial in a different unit. Since 2013, TOPS has come within the remit of the National Health Service's Health Research Authority, and registration of individual healthy volunteers has become a standard condition of ethical approval, as well as part of the Medicines and Healthcare products Regulatory Agency (MHRA) accreditation scheme. Healthy volunteers are identified by their National Insurance number (for UK citizens) or by their passport number and country of origin (for non-UK citizens). TOPS includes information about the date of the last dose of study medicine received, but does not include information about payments made to healthy volunteers or about post-study exclusion periods.



Other examples of volunteer registries include the Swiss Canton of Ticino, which set up a mandatory government-run registry for healthy volunteers in the early 2000s. The Clinical Research Subject Verification program "ClinicalRSVP", in the USA, and Verified Clinical Trials in Canada are further examples of volunteer registries, but are both privately managed. US researchers have advocated that a national registry could play an important role in promoting research integrity *and* protecting subjects from harm [Motluk, 2009; Kupetsky-Rincon et al., 2012; Resnik & McCann, 2015].

Cap scheme for monetary incentives

To date, the French national registry, the *Volontaires Recherche Biomédicale*, is the only scheme which operates a cap scheme for monetary incentives. The amount of financial incentives received for each study is entered into the national registry, and a maximum level of earnings is set by law, currently 4,500 Euros over 12 months.

Recommendations

1. Promote the establishment of National Healthy Volunteer Registries in countries where Phase 1 clinical trials are carried out.

    - The recommendation is particularly pressing for the USA, China, Mexico and the Republic of Korea, who have the highest number of Phase 1 clinical trials according to our survey.

2. Encourage the adoption of a cap scheme for monetary incentives as part of the National Healthy Volunteer Registries.

Outcomes if Recommendations are enacted

1. Serious medical conditions or even lethal harm to healthy volunteers could be minimized by preventing undetected participation in simultaneous studies.

2. Invalid scientific study results, which could also harm future patients, could be minimized by preventing multiple enrolment of professional volunteers.

3. A highly desirable benefit of National Healthy Volunteer Registries would be the availability of data on healthy volunteers to enable the adaption of protective measures for this group.

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Reviewers and Editing Support

Thanks to Julie Cook, Doris Schroeder, Rachel Wynberg and Dafna Feinholz for reviewing the policy brief and to Julie Cook and Doris Schroeder for providing editorial support.

Acknowledgements

Thanks to the TRUST Healthy Volunteer Group for support throughout: Dr Vasantha Muthuswamy (FERCI), Dr Urmila Thatte (FERCI), Dr Dafna Feinholz (UNESCO), Prof. Doris Schroeder (UClan), Prof. Klaus Leisinger (FGVA) and the Sanofi Bioethics Committee's chairperson, Dr Ameet Nathwani.

Citing Suggestion

Francois Bompart and Francesca I Cavallaro (2018), *Policy Brief: Healthy Volunteers in clinical research: making participation safe, fair and transparent*, a report for TRUST, available: http://trust-project.eu/deliverables-and-tools/.

This Brief was provided as part of the TRUST Project, as Deliverable 6.1, grant agreement 664771.