THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 14 Issue 2

RESEARCH ARTICLE

Over-volunteering in Phase I clinical trials: data from a healthy volunteers' registry in Japan

Hiroyuki Fukase[1*], François Bompart[2], François Hirsch[2], Yuji Kumagai[3]

[1]Clinical Research Hospital Tokyo, Tokyo, Japan
[2]Inserm Ethics Committee, Paris, France.
[3]Kitasato University Kitasato Institute Hospital, Tokyo, Japan

[*]Hiroyuki.fukase@crht.jp

OPEN ACCESS

PUBLISHED
28 February 2026

CITATION
Fukase, H., Bompart, F., et al., 2026. Over-volunteering in Phase I clinical trials: data from a healthy volunteers' registry in Japan. Medical Research Archives, [online] 14(2). https://doi.org/10.18103/mra.v14i2.7231

DOI
https://doi.org/10.18103/mra.v14i2.7231

ISSN
2375-1924

ABSTRACT

Background. Over-volunteering refers to situations where healthy human volunteers (HVs) participating to clinical trials do not respect exclusion periods between trials, usually to maximize financial gains. By doing so, HVs expose themselves to potential safety risks and may compromize the trials' data integrity. The extent of this phenomenon is poorly documented in the scientific litterature.

Objectives. We sought to estimate the rate of over-volunteering based on trial enrollment data collected since 1995 by the Japan Association of Contract Institutes for clinical Pharmacology (JACiC) . We also sought to review key issues related to over-volunteering and to reflect about effective systems that could address this phenomenon around the world.

Methods. Our study is based on yearly data on trial enrollment between 2004 and 2023 at participating Clinical Research Units (CRUs) published on the website of the JACiC. We focus on the number of over-volunteering attempts detected by JACiC's Subject Matching System in healthy volunteers studies as data reflecting the reality of over-volunteering in Japan. We examine the Over-Volunteering Prevention Service (TOPS) in the UK as another example of functioning registries.

Results. Out of a total of more than 860,000 HVs screened for participation in approximately 20 Phase I research units for 20 years, we found rates of over-volunteering sustained at relatively constant levels around 2 to 3% every year, including during the COVID-19 pandemic 2019 to 2021 period. This stable rate of over-volunteering attempts contrasts with the data from a single research site in the UK where the TOPS system was implemented and progressively decreasing over-volunteering rates were observed over time.

Conclusions. The JACiC data published here are the first to provide objective evidence on its frequency through over 20 years of data collection in Japan and show the significant and stable occurrence of this phenomenon. To assess between-country differences in over-volunteering rates, collection and publication of similar data from other countries, including from privately-operated registries, would be very valuable. Finally, consideration should be given to the implementation of compulsory HV registries on a national or multinational basis as the best way to prevent over-volunteering and its detrimental effects on HVs safety and on scientific data integrity.

Keywords: Phase I clinical trials, healthy volunteers, over-volunteering, VOLRETHICS, national registries.

1. Introduction

The involvement of healthy human volunteers (HVs) in Phase I clinical trials, including first-in-human administrations of investigational drugs, is well known. However, HVs are also involved in many other types of clinical trials such as pharmacokinetic studies of approved pharmaceuticals such as bioavailability and bioequivalence studies for the development of generic formulations. They are also increasingly involved in the development of new drug modalities such as monoclonal antibodies and nucleic acid drugs, anti-cancer drugs such as immunomodulators and molecularly targeted drugs with better safety profiles than chemotherapy drugs. Protecting HVs from adverse events is of utmost importance as their benefit/risk balance differs markedly from that of patients involved in research. The term "over-volunteering" is used to describe situations where HVs do not respect exclusion (or "wash-out") periods between trials to maximize financial gains. By over-volunteering, HVs may compromise their health and well-being but also the integrity of the study data. This phenomenon is very poorly documented in the scientific literature. We report here data from the Japan Association of Contract Institutes for clinical Pharmacology (JACiC)'s Subject Matching System: involving more than 860,000 HVs screened for participation in approximately 20 Phase I research units in Japan over 20 years. This article aims at reviewing key issues related to healthy volunteers' over-participation in clinical trials and to reflect about effective systems that could address this phenomenon around the world.

Although our focus is solely on JACiC's data, implications of our findings extend beyond these borders, impacting future directions in mitigating risks surrounding participants and ensuring scientific data integrity in clinical trials.

2. Objectives of Clinical Trials involving Healthy Volunteers

The involvement of healthy volunteers (HVs) in first-in-human Phase I clinical trials of investigational drugs is well recognized. This strategy potentially allows for early clinical characterization of pharmacokinetic parameters and clinical safety profiles in the absence of confounding factors such as comorbidities and concomitant medications. In addition, it may be possible to eliminate site-to-site procedural variability since Phase I trials with HVs can often be completed at a single site. The primary objectives of Phase I clinical trials are to investigate the pharmacokinetics and pharmacodynamics of new drug candidates, determine appropriate dosing, and confirm safety and tolerability. However, healthy volunteers are involved in many clinical development steps beyond actual Phase I trials and the term "Phase I" has implicitly evolved to refer to all trials involving healthy research participants as opposed to patients. It is not possible to have a clear view of the number and types of studies involving HVs around the world, but is has been estimated that around 90% of trials involving HVs are not "first-in-man" administrations of novel compounds, but rather bioavailability, bioequivalence and other clinical pharmacology studies to evaluate pharmacokinetics, drug metabolism, food effects, potential drug-drug interactions, the effects of hepatic and renal dysfunction, and other pharmacological parameters essential for the development of pharmaceutical products and pharmacogenetic considerations[1-4].

In recent years, not only conventional small molecule drugs but also new drug modalities such as monoclonal antibodies and nucleic acid drugs have been studied in phase I clinical trials in healthy volunteers[5-8]. Furthermore, recent scientific advances in cancer research have led to the development of immunomodulatory drugs and molecularly targeted drugs with superior safety profiles compared to chemotherapy drugs, making it possible to enroll healthy volunteers (HVs) in clinical trials[9-13]. The safety risks to HVs in early-phase trials are now becoming increasingly diverse due to the diversity of drugs being tested and the resulting complexity of trial designs[14].

3. Healthy Volunteers as Participants in Clinical Trials

Healthy volunteers are, by definition, healthy people with no known medical conditions relevant to the purpose of the study. They are also defined as individuals who understand the study key features and can voluntarily consent to participate. Unlike patients with relevant diseases who participate in clinical trials, healthy volunteers in

the majority of studies cannot expect to receive any direct medical benefit from the treatment being tested[15]. HVs typically spend days to weeks at a residential research facility, allowing for extensive pharmacokinetic sampling plans and more in-depth safety monitoring and management of clinical pharmacology trials requiring crossover designs and long washout periods can be very challenging for patients, but are standard in HVs[4]. Likewise, constraints are imposed on HVs during clinical trials, such as dietary and exercise limitations, isolation from friends and family, multiple safety checks, biological samples collections, site visits, etc. These constraints are implemented to ensure the safety of the HVs and the quality of the study data but it is important to realise that they may have consequences on the well-being of HVs, in ways that are very different from that of patients who participate to research[23]. Overall, healthy volunteers who participate in biomedical research are exposed to a variety of risks different from those of patients, including risks to their rights, their own health and well-being, as well as risks of exploitation based on their economic status, education level, and motivations[16].

4. Over-volunteering

The term over-volunteering has been coined to describe situations where, to maximize payments, some volunteers participate in multiple studies simultaneously or without observing the required washout period between them[17,18]. As a rule, information and informed consent documents specifically state washout periods among trial exclusion criteria. Some HVs deliberately ignore this issue when they attempt to over-volunteer, while other may misunderstand instructions about intervals between trials or overestimate the interval since their last trial[19]. By doing so, they expose themselves to safety risks because of potential drug-drug interactions but also jeopardize the scientific integrity of the collected study data. Over-volunteering is a concealed phenomenon and therefore extremely difficult to assess. To our knowledge, only one scientific paper reports attempts at quantitatively documenting this issue. That is the 2012 paper by Boyce et al.[19] which reports on the early days' experience of the UK over-volunteering prevention system (TOPS) that is further described in this paper. Boyce at al report data from one of the participating sites on the number of detected over-volunteering attempts in the period 1997–2011. Every year, between 767 and 1811 HVs were screened for participation. In the first 2 years after TOPS started being used (2002), potential over-volunteering rates increased from about 1% to a peak of 4.6%. There was a progressive fall in the following years, and in the last few years the reported incidence was less than 1%, presumably as HVs became increasingly aware of the existence of TOPS. As the authors state "TOPS not only helps to prevent overvolunteering, but also deters subjects from trying to do so". Overall, though, over-volunteering in HVs is a poorly documented issue in the scientific litterature.

5. Over-volunteering data from the JACiC

In 1991 a "Subject Verification System" operated by the Japan Association of Contract Institutes for clinical Pharmacology (JACiC) was set up to detect potential over-participation of human research participants. It started being used by 13 clinical research units (CRUs) and is currently used on a voluntary basis by nearly 30 of the public and private CRUs that are members of JACiC. These represent a large majority of the CRUs in Japan, but do not include units dedicated to bioequivalence studies for generic drugs. Some medical institutions and clinical trial sponsors do not use the JACiC database, primarily because its usage requires payment of a yearly fee[20]. The system collects only basic data on potential healthy research participants: name, date of birth, last administration date of the study drug, last observation date, and acceptable date of next participation. Data are not anonymized, but personal data are automatically erased after 2 years. The system can be used by accredited users only. Table 2 in Appendix shows the number of CRUs using the JACiC database between 1995 and 2023.

The Subject Verification System includes since its beginning a feature called "Subject Matching System" which aims at detecting attempts at over-participation by comparing a given subject's exclusion period with that of the planned new trial. Standard washout period between trials is set at 4 months in Japan. Investigators can adapt this period as needed in the Subject Verification System depending on the pharmaceuticals

administered to each individual HV. Table 1 shows the total number of HVs screened between 2004 and 2023 by the participating CRUs through the Subject Matching System, the number of cases of detected double registration (that is persons at risk of over-volunteering for not respecting exclusion periods), and the numbers eventually enrolled in trials based on all inclusion/exclusion criteria, including respect of wash-out periods. Data before 2004 are no longer available for analysis.

Table 1 Number of over-volunteering attempts detected in the healthy volunteers studies carried out at CRUs member of JACiC

Year	Volunteers screened	Volunteers enrolled	Detected over-volunteering attempts (% of volunteers screened)
2004	34,460	8,322	1,354 (3.92%)
2005	35,946	7,389	1,107 (3.07%)
2006	41,567	9,466	1,350 (3.24%)
2007	42,283	8,955	1,326 (3.13%)
2008	39,564	9,035	1,038 (2.62%)
2009	38,543	9,237	989 (2.56%)
2010	46,124	12,544	1,030 (2.23%)
2011	48,775	12,436	840 (1.72%)
2012	54,847	14,897	1,380 (2.51%)
2013	58,095	15,972	1,123 (1.93%)
2014	48,858	13,917	1,096 (2.24%)
2015	59,178	17,113	1,369 (2.31%)
2016	47,058	11,943	1,754 (3.72%)
2017	42,094	11,916	743 (1.76%)
2018	40,738	11,538	933 (2.29%)
2019	36,653	9,037	928 (2.53%)
2020	43,034	11,035	1,180 (2.74%)
2021	38,441	11,284	1,042 (2.71%)
2022	30,462	8,107	909 (2.98%)
2023	39,814	10,928	894 (2.24%)
Total	866,534	225,071	22,385 (2.58%)

Data are available from JACiCA's homepage. 20

It is interesting to notice that over the 20 years reported here, including the COVID-19 pandemic 2019 to 2021 period, the number of screened subjects remained overall stable, as well as rates of over-volunteering, at around 2 to 3% every year. This stable rate of over-volunteering attempts contrasts with the experience of Boyle et al, where awareness of the registry seems to have played a role in progressively decreasing over-volunteering rates over time. This difference might be due to the fact that data from the UK concerned a single research site where potential HVs became increasingly aware of the implementation of the TOPS system, whereas the JACiC system is less widely known from Japanese HVs.

6. Risk Assessment in Clinical Trials

The ethical guidelines for clinical research established in the Declaration of Helsinki state that "Medical research involving human participants may only be conducted if the objective outweighs the risks and burdens to the research participants" (WMA, 2024). Research involving human subjects must be carried out in ways that minimize risks, or at least ensure that all adverse effects are known and predictable, with clear knowledge of how to manage them. Therefore, on a case-by-case basis, researchers must identify and minimize the risks posed by the trial and its research interventions, and determine whether they are justified by the potential benefits of the research. It goes without saying that safety of human participants is the first priority in all cases.

The risk identification process involves two axes of evaluation:

1. What is the likelihood that participation will pose a risk, and what measures are being taken to minimize such risks?

2. What is the magnitude of the anticipated risks of participation, and are they justifiable or avoidable?

Researchers must take all steps to address identified risks. Strictly defined exclusion criteria must be used to eliminate candidates who may be at increased risk[21]. An important feature of actual Phase I clinical trials is that they are designed to detect early safety signals. As detailed by Jill Fisher, specific ethical issues arise from the fact that healthy study participants are deliberately exposed to increasing doses of pharmaceuticals to enable detection of safety issues that would be more complex, longer and more expensive to assess in patients[22].

7. Healthy Volunteers' Understanding of Risk

Participants in Phase I healthy volunteer trials are financially compensated for their time and for the study constraints. As explained later, precautions must be taken for financial compensation not to become an undue inducement for trial participation. Nevertheless, there is no doubt that the perspective of financial gains may affect the HVs' assessment of the risks they are exposed to in participating in a trial. These characteristics of Phase I HV trials create a research environment that is significantly different from clinical studies in patients who only get limited compensation for the expenses they may incur because of the research, exposing to the risk of enrollment of a disproportionate ratio of economically disadvantaged participants among HVs[23-26]. It has been reported that HVs often perceive the overall risk of Phase I trials differently from their own personal risk of harm. Although the majority of participants view Phase I trials as carrying some level of risk, most hold contradictory views that they will not be personally harmed[17]. A US study on the perception of risks by HVs concluded that the most structurally disadvantaged HVs can come to feel not exploited or endangered but grateful for the economic opportunity to participate in clinical trials [27].

8. Monetary Rewards As the Primary Motivator for Volunteers to Participate in Clinical Trials

Systematic studies examining volunteer motivation have revealed that monetary rewards are not the only, but consistently the primary motivator for HVs to participate in clinical trials[28-31,26]. Monetary rewards as compensation for study constraints may undermine HVs' ability to freely participate in research and may jeopardize the principle of autonomy, one of the fundamental principles of bioethics[32]. In resource-limited settings, HVs are often poor and illiterate, do not understand the risks they may be taking, and are in no position to refuse financial incentives. For many of them, clinical trial participation is an important source of income. Economically disadvantaged groups tend to participate in more clinical trials and stay longer than more advantaged groups[33]. This may lead them to secretly participate in multiple studies simultaneously to increase their income. Many repeat volunteers have become adept at manipulating screening tests for clinical trial participation by developing tactics to conceal their simultaneous participation in multiple studies, medical conditions, concomitant medications, or substance abuse. Such concealment not only exposes volunteers to medical risks (e.g., drug interactions), but also potentially biases study data, including the safety and pharmacokinetic profiles of the drugs being tested[34,35].

9. Risk of Undue Inducement

A delicate balance exists between fair financial compensation and undue financial inducement. Subjects, particularly those in Phase I trials whose health will not directly benefit from the study, routinely receive financial compensation for study-related constraints and dedicated time. However, if the amount paid is too high, it may induce potential subjects to participate in the study against their own judgment. All precautions must be taken to minimize safety risks and higher potential risks cannot equate higher rewards. Compensation amounts must only be based on the constraints that the study imposes on HVs. Researchers and research ethics committees should carefully consider regulatory guidelines regarding appropriate compensation for research participation without jeopardizing volunteers' autonomy and ability to make the right choices.

In some but not all countries, research ethics committees may refer to guidelines regarding appropriate payments for various studies and procedures and are asked to ensure that payments do not exert undue influence[36]. In particular, excessive compensation that may encourage HVs in phase 1 trials to conceal information that would disqualify them from participating in the study[37].

Financial rewards for HVs need to be carefully adjusted to balance the risk of exploitation (paying too little) with the risk of undue influence (paying too much), ensuring that volunteers are fairly compensated for their time and effort. Increasing compensation levels could potentially broaden participation among higher-income groups who currently do not perceive compensation as sufficient to justify their participation[38]. To avoid the risk of undue inducement, the 1988 French law which created the national HVs' registry imposes a maximum amount of compensation that can received by a HV per year. It was last revised in 2023 and set at 6000 Euros[39].

In most countries, laws and regulations for the protection of HVs in drug research are lacking, as they have been designed primarily for the protection of patients involved in research. This also translates into lack of specific gudelines for ethics research committees that are tailored to the specific protection needs of HVs. One of the main shortcomings of this situation is insufficient oversight of the scientific validity of research protocols, ethical review, and financial incentives that are specific to HVs. Of particular importance for ethics review committees are the procedures for obtaining genuinely informed consent as well as those for financial compensation payments which must be fair to all involved and must not restrict the volunteers' autonomy or undermine the objectives of the research[40]. Because compensation for Phase I trials marks a significant difference between HVs and patients involved in later-stage trials, researchers have stressed the need to avoid unfair incentive for participants to accept risks that they would not normally accept, including risks related to participation in multiple consecutive trials[41].

10. Healthy Volunteers Registries

Two pillars of ethical and safe participation of HVs in clinical trials are the collection of a properly obtained informed consent and steps to minimize exposure to risks, including avoiding concealed participation in multiple trials. Obtaining valid consent is crucial to respecting HVs' autonomy, as it gives them the opportunity to choose to participate in research and voluntarily accept the potential associated risks. It is the researcher's responsibility to ensure that informed consent documents and procedures contain effective elements that ensure volunteers are making an informed choice about participating in the research[42]. These elements must include information on the exclusion period to be respected between consecutive trials. However, as explained above, HVs may not always respect or understand this requirement and expose themselves to the risks related to over-volunteering. To address these risks, 3 countries to date have set up compulsory HVs registries: France since 1988, the UK since 2013 and Malaysia since 2021.

A recent article has reviewed the key features of each of these registries[18]. As an example of functioning registries, the UK has set up a national participant database called The Over-Volunteering Prevention Service (TOPS). This system is managed and administered by the MHRA (Medicines & Healthcare products Regulatory Agency). Currently, to receive REC (UK Research Ethics Committees) approval, trials involving healthy participants must enroll participants in TOPS. Organisations must maintain a a comprehensive list of all participants who have taken part in clinical trials, which will enable them to identify when any UK research center last dosed a participant. Procedures for managing databases comply with the latest data protection regulations. Any decision to use medical records or TOPS must be documented (e.g., as part of a risk assessment)[43]. TOPS is internet-based, simple, quick to use, and free to users. As mentioned earlier, an early version of TOPS used at a single facility was reported to have reduced the rate of subjects volunteering within three months of completing another study elsewhere to less than 1%[19]. WHO officials in charge of the International Clinical Trials Registry Platform (ICTRP) have expressed willingness to provide assistance to countries for setting up their own HV registry (pers. comm).

Except for France, the UK, and Malaysia, other countries lack a central system to detect and prevent over-volunteering. Furthermore, no country limits the number of clinical trials allowed per HV or the amount of compensation participants can receive per year (except for France with a 12-months maximum of 6000 Euros). As a result, many countries have unknown numbers of "professional healthy volunteers" who, to optimize their financial gains may circumvent protections designed to minimize the risk of harm and ensure the integrity of research[44-47].

While, privately-operated registries such as India's biometric system and the US's Verified Clinical Trials are used by some clinical research units (mainly private contract research organizations), their use is not universally mandatory within countries, much less between countries. Anecdotal evidence was reported that some experienced HVs easily cross country borders between countries[19], or states in federal countries, looking for the best paid clinical trials. Looking for sites with the highest potential financial gains has always been an objective of "professional" healthy volunteers which has become much easier in recent years with the development of social media[48]. Detailed arguments have recently been put forward by Abadie et al. for the widespread implementation of mandatory registries to protect HVs and to increase the transparency, reliability, and integrity of trial results, contributing to the development of safer and more effective medicines[61].

11. Over-volunteering and the VOLRETHICS initiative

Despite a few published empirical studies and ethical analyses of research involving HVs, there have been few concerted efforts to change the way research involving HVs is overseen and regulated[49-52]. Because the risk-benefit balance is different in trials involving healthy people as compared to patients, specific guidelines are needed for trials involving HVs. Healthy volunteer trials are not always perceived as essential as patient trials, and some people consider them a necessary evil, which may be the reason why specific guidelines have not been put forward. In addition, unlike patients who are more and more considered as active participants in research, HVs are not organized in support groups to get their voices heard. A new collaborative effort to better protect and empower HVs globally is the VolREthics initiative, which has evolved in July 2025 into the non-profit VOLRETHICS Association. Launched in 2022, the initiative brings together the international community to address how to better protect HVs from risks of harm and exploitation and safeguarding the validity of clinical trials[52,53].

Drawing on the experiences of stakeholders around the world, from those who conduct clinical trials to those who study and monitor how they are conducted, including HVs from several countries, a Global Ethical Charter for the Protection of Healthy Volunteers in Clinical Trials was published in 2024. It aims at supplementing existing global provisions on the protection of human research participants such as the ICH guidelines and Declaration of Helsinki ethical issues that are specific to HVs. The Charter defines 15 rights to which HVs are entitled[45,54]. One of the key issues addressed in the Charter is the risk of over-volunteering, addressed through Article 10 which states "*Preventing over-volunteering, i.e. not respecting exclusion (or "washout") periods between trials, is crucial to protect participants and the integrity of clinical trials. 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*".

In all its articles, the Global Ethics Charter highlights key issues and proposes ways to address them but relies on local stakeholders to decide on the level of importance and the practical implementation of its 15 recommendations.

12. Potential disadvantages of Introducing Volunteer Registries

The lack of data on the adverse events associated with over-volunteering and the lack of evidence on the cost-effectiveness of implementing nationwide HV registries may be considered as reasons for postponing decisions on their implementation. However, like all concealed phenomenons, over-volunteering cannot be accurately measured, only roughly assessed and partially prevented. Another argument against national registries could be that implementing stricter safeguards in some countries could incur additional costs for sponsors, leading them to conduct their studies in countries with less stringent regulatory protections. This could also encourage some HVs to travel to countries with less stringent regulatory protections in order to receive higher compensation through concealed repeated participations[18]. These are the reasons why the Global Ethics Charter calls for systems that

operate across national borders and avoid different protection standards between countries. A global, international system for protecting all human research participants, including HVs, would be highly desirable[55,56] but it would be extremely complex to design and its implementation would require a level of international cooperation that is difficult to conceive in the foreseeable future because of differences in regulations between countries on issues such as the protection of personal data, the existence or not of national identification numbers, accreditation of research sites, etc.[18]

13. Conclusion

Over-volunteering is a concealed phenomenon which consequences on participants' safety and data integrity cannot be measured, but which can be prevented at least partly. The JACiC data published here are the first to provide objective evidence on its frequency through over 20 years of data collection in Japan and show the significant and stable occurrence of this phenomenon. Use of the JACiC registry protected hundreds of HVs from the risks of over-volunteering. A broader use of this registry across research sites in Japan should be encouraged to more comprehensively protect HVs across the country. To assess between-country differences in over-volunteering rates, collection and publication of similar data in other countries, including from privately-operated registries, would be very valuable. We also submit that consideration should be given to the implementation of compulsory HV registries on a national or multinational basis as the best way to prevent over-volunteering and its detrimental effects on HVs safety and on scientific data integrity. Given the globalization of clinical trials, it might be worth considering to incorporate this topic into ICH guidelines to encourage countries where no national registries are implemented to introduce mandatory systems to prevent over-volunteering.

Conflict of Interest Statement:

The authors declare no conflicts of interest.

Funding Statement:

The authors have nothing to report.

Acknowledgements:

None.

Author Contributions

All authors conceptualized the manuscript and all provided significant inputs. H.F. wrote the manuscript, and all authors reviewed, edited and approved the manuscript.

References:

1. Karakunnel JJ, Bui N, Palaniappan L, Schmidt KT, Mahaffey KW, Morrison B, Figg WD, Kummar S. Reviewing the role of healthy volunteer studies in drug development. J Transl Med. 2018;16:336. doi: 10.1186/s12967-018-1710-5. PMID: 30509294 ; PMCID: PMC6278009.

2. Cherian JJ, Poomali A, Mukherjee A. Increasing early phase clinical trials capacity in India. Communications Medicine. 2025;5:255. doi:10.1038/s43856-025-00970-z

3. Bende B, Németh A. EARLY PHASE TRIALS. Curriculum Development of Human Clinical Trials for the Next Generation of PhD Students and Early Career Researchers in the Medical, Science, Pharmacy and Health Professions. 2024.

4. Bompart F. Healthy volunteers for clinical trials in resource-poor settings: national registries can address ethical and safety concerns. Camb Q Healthc Ethics 2019; 28(1): 134–143.

5. Tranter E, Peters G, Boyce M et al. Giving monoclonal antibodies to healthy volunteers in phase 1 trials is it safe? Br J Clin Pharmacol. 2013;76:164–172. doi: 10.1111/bcp.12096

6. Willmann S, Marostica E, Snelder N, Solms A, Jensen M, Lobmeyer M, Lensing AWA, Bethune C, Morgan E, Yu RZ, Wang Y, Jung SW, Geary R, Bhanot S. PK/PD modeling of FXI antisense oligonucleotides to bridge the dose-FXI activity relation from healthy volunteers to end-stage renal disease patients. CPT Pharmacometrics Syst Pharmacol. 2021 Aug;10(8):890-901. doi: 10.1002/psp4.12663. Epub 2021 Jun 23. PMID: 34085768; PMCID: PMC8376138.

7.Geretti AM, Sostelly A, Buatois S, Lu S, Lemenuel A, Attley G, Bopst M, Alvarez-Sánchez R, Mueller H, Gane E.2025.Safety, pharmacokinetics, and pharmacodynamics of the antisense oligonucleotide RO7239958 in healthy volunteers and adults with chronic hepatitis B infection. Antimicrob Agents Chemother69:e00679-25. https://doi.org/10.1128/aac.00679-25

8.Han K, Theodore D, McMullen G, Swayze E, McCaleb M, Billioud G, Wieland S, Hood S, Paff M, Bennett CF, Kwoh TJ. Preclinical and Phase 1 Assessment of Antisense Oligonucleotide Bepirovirsen in Hepatitis B Virus-Transgenic Mice and Healthy Human Volunteers: Support for Clinical Dose Selection and Evaluation of Safety, Tolerability, and Pharmacokinetics of Single and Multiple Doses. Clin Pharmacol Drug Dev. 2022 Oct;11(10):1191-1202. doi: 10.1002/cpdd.1154. Epub 2022 Aug 16. Erratum in: Clin Pharmacol Drug Dev. 2025 Oct 27. doi: 10.1002/cpdd.1620. PMID: 35971951; PMCID: PMC9804925.

9. Omes-Smit G, Garsen M, Zwiers A. Healthy Volunteer Studies in the Development of Anticancer Drugs with Genotoxic Findings. Ther Innov Regul Sci. 2022;56:76-84. doi: 10.1007/s43441-021-00330-8. Epub 2021 Aug 11. PMID: 34379306; PMCID: PMC8688384.

10. Radanovic I, Klarenbeek N, Rissmann R et al. Integration of healthy volunteers in early phase clinical trials with immuno-oncological compounds. Front. Oncol. 2022; 12: 1-18. doi: 10.3389/fonc.2022.954806

11. de Las Heras B, Bouyoucef-Cherchalli D, Reeve L, Reichl A, Mandarino D, Flach S, Vidal L, van Brummelen EMJ, Steeghs N. Healthy volunteers in first-in-human oncology drug development for small molecules. Br J Clin Pharmacol. 2022;88:1773-1784. doi: 10.1111/bcp.15092. Epub 2021 Oct 19. PMID: 34558113; PMCID: PMC10234445.

12. Drezner N. Regulatory Challenges In the Use of Healthy Volunteers. 2018. https://www.ascpt.org/Portals/28/docs/Annual%20Meetings/2018%20Annual%20Meeting/Presentations/March%2023%202018/Drezner_%20Nicole%20Healthy%20Volunteers%20ASCPT.pdf?ver=2018-04-12-195032-280

13. Courville J, Barber A, Fura A. Navigating First-in-Human and Early-Phase Patient Studies Study Designs, Risk Mitigation, and Population Selection Challenges J Clin Pharmacol. 2025;65:835-849. doi: 10.1002/jcph.70002.

14. Lorch U, Vincent C. The safety of early phase clinical trials Bridging the gap between governance and practice. Br J Clin Pharmacol. 2024;90:1538–1540. doi: 10.1111/bcp.16141

15. Bompart F, Fisher JA, Allen E et al. The VolREthics initiative to protect the well-being of healthy volunteers in biomedical research. Nat Med. 2023; 29: 2393–2394. doi.org/10.1038/s41591-023-02490-6

16. Karkar M, Lemaitre C, Bompart F et al. Healthy volunteers' protection around the world. Med Sci (Paris). 2023; 39: 769-775. doi: 10.1051/medsci/2023118

17. Fisher JA, McManus L, Wood MM et al. Healthy Volunteers' Perceptions of the Benefits of Their Participation in Phase I Clinical Trials. J Empir Res Hum Res Ethics. 2018; 13: 494–510. doi:10.1177/1556264618804962

18. Abadie R, Fisher JA, Mwale S, Bompart F, Hirsch F. Policy recommendations for implementing registries to minimize over-volunteering in Phase I clinical trials. Clin Trials. 2025;22:757-760. doi: 10.1177/17407745251360649. Epub 2025 Jul 29. PMID: 40727967.

19. Boyce M, Walther M, Nentwich H et al. TOPS: an internet-based system to prevent healthy subjects from over-volunteering for clinical trials. Eur J Clin Pharmacol. 2012;68: 1019-1024. doi: 10.1007/s00228-012-1231-8

20. Number of double registration prevented cases. https://jacicp.jp/subject-verification-system/double-medication-prevention-count-1.html

21. Emmanuel OA. ETHICS OF TRIALS IN HEALTHY VOLUNTEERS. South American Journal of Clinical Research. 2025; 2.

22. Fisher JA. Adverse events: race, inequality, and the testing of new pharmaceuticals. New York University Press. 2020.

23. Yu H, Fang Y,Qi X et al. Sociodemographic characteristics of healthy volunteers along with their experience, attitude and concerns of clinical trials in Wuhan, China. Sci Rep. 2023;13:19550. doi: 10.1038/s41598-023-46979-z

24. Walker RL, MacKay D, Waltz M, Lyerly AD, Fisher JA. Ethical Criteria for Improved Human Subject Protections in Phase I Healthy Volunteer Trials. Ethics Hum Res. 2022;44:2-20. doi: 10.1002/eahr.500139. PMID: 36047278; PMCID: PMC9931499.

25. Seo JH, Kim OJ, Yoo SH. A Study on the Characteristics of Healthy Volunteers who Participate in Phase I Clinical Trials in Korea. J Empir Res Hum Res Ethics. 2022;17:193-212. doi: 10.1177/15562646211034275

26. Ranjan R, Agarwal NB, Kapur P et al. Factors Influencing Participation Of Healthy Volunteers In Clinical Trials: Findings From A Cross-Sectional Study In Delhi, North India. Patient Preference and Adherence. 2019;13:2007–2015. doi: 10.2147/PPA.S206728

27. Cottingham MD, Fisher JA. Risk and Emotion Among Healthy Volunteers in Clinical Trials. Soc Psychol Q. 2016 Sep;79(3):222-242. doi: 10.1177/0190272516657655. Epub 2016 Jul 29. PMID: 28867852; PMCID: PMC5580945.

28. Ji-Hye S, Ock-Joo K, Eun KC et al. Comparison of the characteristics of healthy volunteers participating in Phase 1 clinical trials in Korea and Japan. Transl Clin Pharmacol. 2025;33: 183-196. doi: 10.12793/tcp.2025.33.e16

29. Stunkel L, Grady C. More than the money: a review of the literature examining healthy volunteer motivations. Contemp Clin Trials. 2010; 32: 342-352.

30. Tishler CL, Bartholomae S. The recruitment of normal healthy volunteers: a review of the literature on the use of financial incentives. J Clin Pharmacol. 2002; 42: 365-375,

31. Grady C, Bedarida G, Sinaii N et al. Motivations, enrollment decisions, and socio-demographic characteristics of healthy volunteers in phase 1 research. Clin Trials. 2017; 14:526-536.

32. Ji-Hye S, Ock-Joo K, Eun KC et al. Comparison of the characteristics of healthy volunteers participating in Phase 1 clinical trials in Korea and Japan. Transl Clin Pharmacol. 2025; 33: 183-196. doi: 10.12793/tcp.2025.33.e16

33. Kalbaugh CA, Kalbaugh JM, McManus L et al. Healthy volunteers in US phase I clinical trials: Sociodemographic characteristics and participation over time. PLoS One. 2021; 16:e0256994. doi: 10.1371/journal.pone.0256994.

34. Leisinger KM, Schmitt KM, Bompart F. Healthy Volunteers in Clinical Studies. Ethics Dumping. 2018; 67-70. doi: 10.1007/978-3-319-64731-9_8

35. Edelblute HB, Fisher JA. Using "clinical trial diaries" to track patterns of participation for serial healthy volunteers in U.S. phase I studies. J Empir Res Hum Res Ethics. 2015; 10:65-doi: 10.1177/1556264614568280. Epub 2015 Jan 20. PMID: 25742668; PMCID: PMC4408988.

36. Emmanuel OA. ETHICS OF TRIALS IN HEALTHY VOLUNTEERS. South American Journal of Clinical Research. 2025; 2.

37. Walker RL, Cottingham MD, Fisher JA. Serial Participation and the Ethics of Phase 1 Healthy Volunteer Research Open Access. The Journal of Medicine and Philosophy. 2018;43: 83–114, doi.org: 10.1093/jmp/jhx033

38. Erik R, Mårten S, Folke S et al. Characteristics, Motivations, and Preferences of Healthy Volunteers

in Phase I Clinical Trials in Sweden. Journal of Empirical Research on Human Research Ethics. 2025;20:59-70. doi: 10.1177/15562646241309142

39.https://www.legifrance.gouv.fr/codes/section_lc/LEGITEXT000006072665/LEGISCTA000006190202/2003-05-27

40. Smith RN. Safeguards for healthy volunteers in drug studies.Lancet. 1975 Sep 6;2(7932):449-50. doi: 10.1016/s0140-6736(75)90856-9. PMID: 51249

41. McManus L, Davis A, Forcier RL et al. Appraising Harm in Phase I Trials: Healthy Volunteers' Accounts of Adverse Events. J Law Med Ethics. J Law Med Ethics. 2019;47:323–333. doi: 10.1177/1073110519857289

42. Emmanuel OA. ETHICS OF TRIALS IN HEALTHY VOLUNTEERS. South American Journal of Clinical Research. 2025; 2.

43. Over-Volunteering (Appendix 1, point 16). MHRA Phase I Accreditation Scheme Guidance FINAL v5 01 April 2025

44. Makadi A. Protection of Healthy Volunteers in Clinical Trials: A Crucial Ethical Commitment. Available from https://pace-cr.com/news/protection-of-healthy-volunteers-in-clinical-trials-a-crucial-ethical-commitment/

45. Fisher JA, Abadie R, Hirsch F. Implementing a Global Ethics Charter to Protect US Healthy Volunteers. American Journal of Medicine. 2025;138: 601-603.

46. Jonnalagadda VG. The Global Ethics Health Charter to Protect Healthy Volunteers: Is the Problem Local or International?. American Journal of Medicine. 2025; 138: E112.

47. The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard. Public Comments submitted: VolREthics initiative – Global Ethics Charter for the Protection of Healthy Volunteers in Clinical Trials March 30, 2024. Available from https://mrctcenter.org/resource/public-comments-submitted-volrethics-initiative-draft-global-ethics-charter-for-the-protection-of-healthy-volunteers-in-clinical-trials/

48. Edelblute HB, Fisher JA. Using ''clinical trial diaries''to track patterns of participation for serial healthy volunteers in US phase I studies. J Empir Res Hum Res Ethics. 2015; 10(1): 65–75.

49. Walker RL, MacKay D, Waltz M et al. Ethical Criteria for Improved Human Subject Protections in Phase I Healthy Volunteer Trials. Ethics Hum Res. 2022; 44:2-21. doi:10.1002/eahr.500139

50. Naseer S. Safety Considerations in Phase 1 Trials. 2024 https://www.fda.gov/media/185120/download

51. Naseer S. Safety Considerations in Clinical Drug Development https://www.fda.gov/media/175394/download. 2023.

52. Fisher JA. Global Efforts to Protect Healthy Volunteers. Hastings Cent Rep. 2023; 53: 2. doi: 10.1002/hast.1494

53. https://volrethics.org/

54. VolREthics A Global Ethics Charter for the Protection of Healthy Volunteers in Clinical Trials June 2024. Available from https://www.inserm.fr/wp-content/uploads/Inserm_VolREthics_EthicsCharterFinalVersion_July24.pdf

55. Aguilera B, DeGrazia D, Rid A. Regulating international clinical research: an ethical framework for policy-makers. BMJ Glob Health. 2020 May;5(5) :e002287. doi: 10.1136/bmjgh-2020-002287. PMID: 32461225; PMCID: PMC7259867.

56. Deiteren A, Coenen E, Lenders S et al. Data driven evaluation of healthy volunteer characteristics at screening for phase I clinical trials to inform on study design and optimize screening processes. Clinical Trial Clin Transl Sci. 2021;14:2450-2460. doi: 10.1111/cts.13113. Epub 2021 Aug 11.

Annex: Table 2 Number of Contract Research Units (CRUs) using the JACiC database between 1995 and 2023 and number of healthy volunteers entered into the database.

Year	Volunteers entered into the database	Participating CRUs
1995	11,409	13
1996	13,585	13
1997	12,688	13
1998	15,742	13
1999	16,051	13
2000	19,882	11
2001	22,801	11
2002	30,050	12
2003	32,267	12
2004	34,460	12
2005	35,946	15
2006	41,567	17
2007	42,283	16
2008	39,564	17
2009	38,543	19
2010	46,124	17
2011	48,775	20
2012	54,874	22
2013	58,095	24
2014	48,858	24
2015	59,178	21
2016	47,058	21
2017	42,094	22
2018	40,738	21
2019	36,653	21
2020	43,034	22
2021	38,441	21
2022	30,462	21
2023	39,814	22