VolREthics
Protecting and empowering healthy volunteers
Inserm

A Global Ethics Charter for the Protection of Healthy Volunteers in Clinical Trials

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HEALTHY VOLUNTEERS' 15 RIGHTS IN CLINICAL TRIALS

To be protected from the risks of harm and exploitation, healthy volunteers are entitled to:

1. Laws and regulations that specifically protect them as research participants,
2. Assurance that their participation in research is ethical and scientifically necessary,
3. Adequate representation throughout the research process,
4. Transparency about clinical trials in which they are involved,
5. Adequate research ethics oversight,
6. Adequate trial site and investigator oversight,
7. Protection from physical harm,
8. Adequate attention paid to their well-being,
9. Adequate protection from potential long-term harm,
10. Protection from the risks of over-volunteering,
11. Recruitment through fair and respectful practices,
12. Relevant study information to provide genuine informed consent,
13. Fair financial compensation for their participation,
14. Post-trial compensation for research-related injury,
15. Adequate processes for confidential reporting of concerns.

Addressing risks of harm and exploitation of healthy volunteers

PREAMBLE

Healthy volunteers contribute to the advancement of science and medicine through their participation in research studies, and their role is well established in the early stages of medicinal product development and pharmacokinetic studies. Beyond this commonly understood role of healthy volunteers, it is important to highlight the involvement of healthy people in many different research fields, at all stages of medicinal product development, vaccine efficacy trials, and medical device development, but also as control subjects in many types of studies; in dietary interventions; epidemiology studies; social, behavioural, and economic science studies; biobanking; environmental exposure studies; etc. The motivations to participate, the risks and benefits to which healthy participants are exposed, and the ethical issues related to so many types of research are too diverse to be addressed in a single Charter.

SCOPE

While we acknowledge the variety of situations in which healthy people participate in research, **this Charter focuses on healthy volunteers involved in interventional clinical trials with medicinal products where there is no potential direct health benefit for the individuals involved.** We adopt this focus because these research studies most often expose healthy volunteers to the **highest risks of harm, exploitation, and compromised well-being**.

Interventional studies in which participants can reasonably hope for health benefits, such as preventive vaccine clinical trials, are excluded. Non-interventional studies are also excluded from the scope of this Charter because the risks related to the participation of healthy volunteers are less pronounced.

RATIONALE FOR THIS CHARTER

The 15 rights to which healthy volunteers are entitled should be applied globally to protect them. As guidance to achieve this outcome, this Charter develops these rights as articles and describes the key principles underlying each right. While these principles should be adhered to as a whole, the way they are implemented in practice may vary from country to country or across research settings. Hence, each of the 15 articles proposes ways to overcome ethical gaps and risks to healthy volunteers as a basis for further development by policy- and decision-makers.

This Charter was developed based on the observation that very few countries have special legal provisions to protect healthy volunteers as a specific type of human research participant. For instance, only France, the United Kingdom, and Malaysia have implemented national participant registries to prevent over-volunteering. Furthermore, internationally accepted reference texts, such as the Declaration of Helsinki, the ICH Good Clinical Practice, and the CIOMS guidelines, were developed to protect all human research participants equally from patients to healthy volunteers, but many of these

documents are virtually silent about the ethical concerns most pertinent to healthy volunteer trials. Despite the importance of these foundational texts in defining ethical principles to protect human research participants, they leave gaps in the protection of healthy volunteers.

Specifically, unlike patients, healthy volunteers:

- Cannot expect direct health benefits from participating in interventional clinical trials, and because they are healthy, any risk of harm results in a very different benefit-risk balance from that of patients;
- Participate in studies usually conducted in residential research facilities with stringent rules and protocols that radically limit their normal routines and may impinge upon their well-being; and
- Are motivated to take part in this type of research primarily because of the prospect of financial compensation, which may expose them to the risk of being exploited when they are in situations of economic vulnerability.

CONTRIBUTION OF CHARTER TO EXISTING ETHICAL GUIDELINES

This Charter takes existing global provisions on the protection of human research participants as a starting point, such that the recommendations outlined here ***are meant to supplement, not replace those ethical guidelines****.* Supporting safe and ethical clinical trials is essential for research validity and integrity and to ensure the social value of research, whereas actions undermining this approach may lead to unethical practices and unreliable results. Based on these considerations, this Charter is organised into three sections:

1. **Laying the foundation to protect healthy volunteers** through specific laws and regulations, adoption of a novel ethical framework for their research involvement, representation of their interests throughout the research process, and transparency about the clinical trials that involve them;
2. **Protecting healthy volunteers from physical and non-physical harm** throughout the clinical trial process by supporting additional research oversight mechanisms and attending to their safety and well-being;
3. **Protecting healthy volunteers from exploitation** when they may be in situations of vulnerability by improving recruitment and consent processes, offering fair compensation for participation, providing post-trial compensation for research-related injury, and addressing healthy volunteers' concerns, wherever applicable.

We do not include here provisions that apply to all participants in clinical studies and have been addressed by existing guidelines and regulations, such as requirements to ensure data confidentiality, return research results to participants, or the management of incidental findings, because this Charter focuses on identifying additional needed protections for healthy volunteers. It is not uncommon for different guidelines or charters to cover similar ethics principles, especially when they relate to foundational principles. Some repetition of principles in this Charter does not invalidate other guidelines but rather underscores the significance of those principles in safeguarding healthy volunteers' safety, well-being, and rights. Such repetition can serve to emphasize the importance of those principles and provide additional clarity and reinforcement in the context of healthy volunteer clinical trials.

OBJECTIVES

Given how very few countries have special legal provisions addressing the risks that healthy volunteers may face when participating in interventional clinical trials, this Charter aims primarily at raising global awareness of these risks and the implications that they may have for medical research processes. It also aims to inform and support healthy volunteers to advocate better for their own protection and well-being. Finally, it aims to encourage countries to adopt specific provisions to protect healthy volunteers.

TARGET AUDIENCE

The recommendations provided in this Charter are primarily intended for policy- and decision-makers entrusted with protecting people's health in the regulation of clinical trials with medicinal products. However, given the crucial role played by other stakeholders, such as commercial and academic sponsors, contract research organisations, ethics review boards, research organisations, regulatory agencies, health professionals, and advocates for healthy volunteers, in defining and implementing ethical and rigorous standards, this Charter is addressed to all stakeholders potentially involved in medical research. This Charter may also apply to other research fields involving healthy volunteers in which potential situations of vulnerability may expose those healthy volunteers to risks of harm and exploitation.

CHARTER DEVELOPMENT PROCESS

This Charter was developed by the VolREthics initiative (Volunteers in Research and Ethics), launched in early 2022 by Inserm, the French national biomedical research agency, with the contribution and support of numerous international partners. It is the result of three international plenary meetings and five regional meetings (Africa, Asia, Europe, Latin America, and North America). A draft version of the Charter was made available in February-March 2024 for public consultation. Comments received were then made public on VolREthics' website and were used to issue a revised, pre-final version of the Charter on April 12, 2024. This document was discussed during the third plenary meeting in Paris (France) with attendees from around the world on April 18-19, 2024. The present version is responsive to comments received during the Paris meeting and was finalized after consultation with an international panel of healthy volunteers.

The Charter was drafted with a focus on the experiences and perspectives of healthy volunteers. Addressing the ethical issues and sources of harm identified by healthy volunteers was crucial to ensuring the representativeness and relevance of the final document. Through a collaborative and inclusive dialogue, the 15 rights to which they are entitled and the content of the 15 articles reflect the needs and expectations of healthy volunteers.

ARTICLES

I. Laying the Foundation to Protect Healthy Volunteers

Article 1: Laws and regulations that specifically protect healthy volunteers as research participants. In line with international ethics standards and with the principles outlined in this Charter, countries should ensure that their laws, regulations, and guidelines that protect research participants include specific provisions for healthy volunteers. These provisions should effectively mitigate the risks of harm and exploitation while fostering healthy volunteers' autonomy to participate in clinical research. Furthermore, laws should include measures to prevent and sanction research misconduct.

Article 2: Assurance that healthy volunteers' participation in research is ethical and scientifically necessary. Countries should put in place measures to ensure that healthy volunteers' involvement in clinical research is always ethical and scientifically necessary. To this end, stakeholders should join efforts to develop and use innovative methods to reduce the number of healthy volunteers involved, refine the methodologies to avoid unnecessary burdens, and replace healthy volunteer studies with alternative methods, when possible.

Article 3: Adequate representation of healthy volunteers throughout the research process. Countries should encourage the formation of groups representing healthy volunteers' interests in the development of laws, regulations, and guidelines designed to safeguard the interests of healthy volunteers throughout the clinical trial process. Ideally, these groups should include past and present healthy volunteers, but other options could be considered to ensure their representation is sustainable over time. Interactions between associations representing healthy volunteers should be facilitated to combat disparities in standards within and across countries, particularly those that could lead to the misuse of populations in lower-income and -resource settings. Clinical trial sites and other stakeholders (e.g., sponsors, ethics review boards) should engage with these representatives to improve the design and conduct of trials with healthy volunteers.

Article 4: Transparency about clinical trials in which healthy volunteers are involved. As is required for later-phase trials, all data, including those from early Phase I trials that involve healthy volunteers, should be made available to the public through existing databases, such as clinicaltrials.gov, the WHO International Clinical Trials Registry Platform, EudraCT (European Union Drug Regulating Authorities Clinical Trials Database), and CTRI (Clinical Trials Registry – India). There is also a need for more public access to data about the number and types of trials involving healthy volunteers globally to enable more research in this field.

II. Protecting Healthy Volunteers from Harm

Article 5: Adequate research ethics oversight. In addition to following existing guidelines and ethical standards, scientific and ethics review boards involved in assessing healthy volunteer trials should possess the necessary expertise, training, and resources to thoroughly assess the quality and integrity of such trials. Board members should understand the risks specific to healthy volunteer trials and how to minimise them. Members should include at least one representative of healthy volunteers' interests who has the requisite knowledge and experience to protect them from harm, ideally from first-hand experience as a healthy volunteer.

Article 6: Adequate trial site and investigator oversight. Countries should establish oversight mechanisms to ensure that sites conducting clinical trials are adequately equipped and staffed with appropriately trained and qualified personnel who will uphold the quality and integrity of the research and safeguard the well-being of healthy volunteers. Oversight should include mandatory inspections of research facilities and review of staff credentials.

Article 7: Protection from physical harm. Risks to healthy volunteers should be minimised through the design of the clinical trials, which should adhere to the latest guidelines on the safe administration of experimental medicinal products and include only medical procedures that are scientifically necessary to address the research questions. The safety of volunteers should be ensured by continuous monitoring for the emergence of adverse events, with access to acute medical care provided throughout the trial.

Article 8: Adequate attention paid to healthy volunteer well-being. It is imperative to prioritize healthy volunteers' well-being during clinical trials. Clinical trial facilities should have sufficient space and be designed to prioritize the safety and well-being of participants. Whenever strict trial conditions are warranted by the study, justification should be given, reviewed, and approved by an ethics review board. To mitigate participants' feelings of isolation, trial sites should provide access to communication technologies, as well as other amenities or activities to enhance well-being during confinement. Additionally, sites should train their staff members to treat healthy volunteers respectfully and to minimise risks of psychological and other non-physical harm and to address such harms promptly whenever they occur.

Article 9: Adequate protection from potential long-term harm. Should any adverse event occur, healthy volunteers must be monitored until either they have returned to their baseline level of health or long-term or permanent changes to their health are acknowledged with an appropriate care plan in place. Regulators and sponsors should implement a system for post-trial, long-term monitoring of adverse events and health care for healthy volunteers. This system should ensure all adverse events that occurred during the trial have been recorded and resolved within the stipulated period and appropriate medical care provided.

Article 10: Protection from the risks of over-volunteering. 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.

III. Protecting Healthy Volunteers from Exploitation

Article 11: Recruitment through fair and respectful practices. Countries should develop frameworks to ensure that recruitment practices for healthy volunteer trials adhere to the highest ethical standards that prevent excessive emphasis on financial compensation, misleading language, and other forms of undue influence. It is also essential to prevent either unjustly targeting or excluding disenfranchised populations, including—but not limited to—financially vulnerable individuals, marginalised communities, the unhoused, and migrants.

Article 12: Relevant study information to provide genuine informed consent. In addition to following all current guidelines and ethical standards, informed consent materials and processes should be tailored to address the specificities of healthy volunteer trials. Information about financial compensation should include details about when and how payment will be made, how compensation will be determined if the study is stopped early or the participant exercises their right to withdraw from the research, and any potential economic risks to participants (e.g., income tax consequences or eligibility for social services). Additionally, detailed information about the risks of failing to follow protocol restrictions, such as dietary requirements and rules about frequency of study enrolment, should be provided.

Article 13: Fair financial compensation for participation. All compensation of healthy volunteers for trial participation has the potential to compromise trial results by incentivizing the concealment of health conditions and adverse events, as well as over-volunteering to earn more income. Countries should develop guidelines on compensation to provide fair and equitable compensation across clinical trial sites. Financial compensation should be reflective of the demands associated with each trial and be approved by ethics review boards. Insufficient compensation for healthy volunteers has the potential to take unfair advantage of lower-income volunteers. Disbursements should be made fairly during the trial, and when offered, completion bonuses to encourage final outpatient study visits should be modest to avoid compromising volunteers' right to withdraw from the trial at any time without prejudice.

Article 14: Post-trial compensation for research-related injury: Healthy volunteers should be protected from the risk of increased financial harm if they experience an injury related to the trial. Because healthy volunteers are healthy, it is imperative to provide, at minimum, compensation in the form of medical care for any research-related injuries that may occur. As with all clinical trials, sponsors and research clinics should have adequate insurance to cover all harms caused by clinical trial participation, from screening through the post-trial period, for injuries related to the clinical trial. There should be a transparent and easily accessible process for healthy volunteers who are harmed in a clinical trial to claim post-trial care and/or financial compensation. The entities responsible for adjudicating whether an injury is trial-related should be independent and without any conflicts of interest.

Article 15: Adequate processes for confidential reporting of concerns. Procedures should be established to allow healthy volunteers to report any concerns to clinical site staff, ethics review boards, or regulatory agencies during and after the clinical trial, without fear of reprisal or loss of entitled financial compensation. Details on how and where volunteers can report concerns should be clearly outlined in informed consent documents. The volunteers' identity should be confidential unless their identity is essential for resolving the complaint and should only be shared with their permission. Participants should be informed about the outcome of any complaints. Written records should be maintained that document reported issues and the corresponding actions taken.

CONCLUSION

This Charter aims to support the global recognition of healthy volunteers as a group of human research participants who deserve specific ethical and regulatory protection. While it focuses on healthy volunteers involved in interventional clinical trials with medicinal products where there is no potential direct health benefit for the individuals involved, we expect that the key principles outlined here may also be relevant to other types of research that involve healthy human research participants.

The Inserm Ethics Committee gratefully acknowledges the support of the many people and institutions that contributed to creating this Charter.

For more information: https://www.inserm.fr/en/ethics/volrethics/