LETTER

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The Global Ethics Health Charter to Protect Healthy Volunteers: Is the Problem Local or International?

To the Editor:

Regarding the article by Fischer et al,[1] a commentary on a global ethics charter to protect healthy volunteers: the authors highlighted the importance of implementing the charter to protect the healthy volunteers who are participating in phase 1 clinical trials in the United States of America. I would like to mention that the phase 1 clinical trials are conducted all around the globe and we should treat everyone participating in India the same way as healthy volunteers are treated in developed countries. India is becoming a center point for conducting clinical trials after the implementation of new drugs and clinical trials (NDCT) rules, 2019,[2] and we might need these rules in the developing countries as well. In addition, as in the United States, India does not have a centralized system of healthy volunteers, and that offers a chance for several "professional healthy volunteers" to participate in different clinical trials without undermining the importance of research ethics and the value of clinical trials because a greater number of participants are illiterate/less educated in nature. Considering these facts, we might need a patient advocacy group, regulatory vigilance, and local administrative support to educate the participants about clinical trials, including developments seen in the Declaration of Helsinki, 2024, by including the term "participants" instead of "subjects."[3] In a nutshell, the healthy volunteers are playing a vital role in clinical development without getting any therapeutic benefit, and we should treat them with more dignity than opposite of "guinea pigs."

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The Reply

In his letter to the Editor related to our Commentary,[1] Mr. Venu Gopal Jonnalagadda raises important issues. Our paper focuses on US healthy volunteers, but many of our considerations apply to India and other countries. This is exactly why the VolREthics Initiative is a global one.[2] Most countries' laws and regulations ignore the specific needs of healthy research participants. In India, the New Drugs and Clinical Trials Rules, 2019 have addressed some of the needs of healthy volunteers involved in Phase 1 and bioequivalence studies, yet some important issues remain, in particular, the risk of over-enrollment due to financial compensation. Indeed, payment for time and inconvenience distinguish healthy volunteers from patients involved in research. Jonnalagadda has mentioned that Indian healthy volunteers, like their US counterparts, are frequently recruited from disadvantaged groups who may be exposed to the temptation of becoming "professional healthy volunteers." Because this is the case in most countries, one of the key recommendations of the VolREthics "*Global Charter to protect healthy volunteers*"[3] is to develop mechanisms to prevent participants' over-enrollment in clinical trials by monitoring and maintaining adequate "wash-out" periods between trials. Failure to respect wash-out periods not only exposes the volunteers to the risk of adverse events but also compromises the integrity of study data. Only the Governments of France, the United Kingdom, and Malaysia have national registries that track healthy volunteers' participation across all research sites. In India, as in the US and some other countries, privately-run registries are available to research sites to check whether participants have adhered to wash-out periods. Still, privately-run registries leave loopholes that enable healthy volunteers to participate in several trials undetected because the use of nationwide registries by all research sites is not mandated by law.

Prevention of over-enrollment is an important issue, but, as we highlight in our Commentary, it is not the only one that needs to be addressed to ensure better protection of healthy volunteers. Because Jonnalagadda refers to the 2024 updated version of the Declaration of Helsinki, we would like to bring attention to the Correspondence titled "Declaration of Helsinki's missed opportunity for healthy volunteer trials" recently published in *The Lancet*.[4] Here we opine that although the revised Declaration of Helsinki explicitly states that it applies to all research participants, it unfortunately does not address adequately the ethical issues specific to healthy volunteers. By focusing on healthy volunteers' specific needs for protection, VolREthics aims at addressing this "blind spot" in biomedical research ethics. Our Commentary here focuses on US healthy volunteers to draw attention to the problems that exist even in Western countries, but we fully support Jonnalagadda's call for global standards in research involving healthy volunteers.

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