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

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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 clearly acknowledged in early stages of medicinal products development. 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 products development, as control subjects, in vaccine efficacy trials, dietary interventions, epidemiology studies, human and social science studies, socioeconomics, biobanks, etc. The motivations to participate, the risks and benefits to which participants are exposed, and the ethical issues related to so many types of research are too diverse to be addressed in a single Ethics Charter.

This Ethics Charter focuses on healthy volunteers involved in interventional clinical trials with medicinal products because these are the research studies in which healthy volunteers are most likely exposed to the highest risks of harm, exploitation, and having their well-being affected.

Unlike patients, healthy volunteers do not expect direct benefit to their health from participating in interventional clinical trials. Additionally, these studies are usually conducted in dedicated facilities with strict rules to follow that radically limit healthy volunteers' normal routines and may compromise their well-being. Moreover, the prospect of financial compensation is most often the key motivation of healthy volunteers to take part in this type of medical research. Therefore, the risk-benefit ratios for them are completely different from that of patients.

Considering that very few countries have special legal provisions addressing the risks that healthy volunteers may face, this Ethics Charter aims to raise attention to these risks and the implications that they may have for medical research processes. Supporting safe and ethical trials is essential for research validity and integrity, while actions undermining this approach may lead to unethical practices and unreliable results.

The recommendations provided in this Charter are primarily intended for policy makers entrusted with protecting people's health in the regulation of clinical trials. However, given the crucial role

played by other stakeholders, such as ethics committees, research organisations, regulators, health professionals, and healthy volunteers, in defining and implementing ethical and reliable standards, this Charter is addressed to all stakeholders potentially involved in medical research and beyond, including all research fields involving healthy volunteers.

VALUING THE DIFFERENCE

Healthy volunteers involved in interventional clinical trials are exposed to (i) risks of harm with no expectation of an immediate benefit for their health; (ii) risk of being exploited when in situations of vulnerability, particularly as a result of financial compensation offered for their participation; and (iii) exposure to the constrained research settings and conditions required by the clinical trials.

The following general recommendations should be taken into considerations to protect healthy volunteers and ensure their well-being.

Article 1. Laws and regulations to protect healthy volunteers. Countries should develop provisions, laws or regulations specifically intended to protect healthy volunteers. These should address the risks of harm and of exploitation, as well as promote healthy volunteers' wellbeing in clinical research.

Article 2. Healthy volunteers' representatives. Countries should support the formation of groups of past and present healthy volunteers to represent their interests in the development of laws or regulations aimed at protecting them, and in key steps of the design, conduct, and closure of the clinical trial process. Interactions with associations representing healthy volunteers should be facilitated to fight double standards, avoid ethics dumping, and to ensure appropriate medical care is provided for anyone harmed by the research.

Article 3. Recruitment practices. Countries should develop frameworks to ensure that recruitment practices adhere to ethical standards that prevent excessive emphasis on financial compensation and misleading language. Specific attention should be paid to prevent targeting disenfranchised populations.

Article 4. Preventing over-volunteering. There should be a mandatory system in place in all contexts of clinical research to prevent over-volunteering (e.g., enrolling in more than one trial at a time or not observing the required "washout" period between studies), within and across national borders. Depending on national/regional circumstances, the system could be managed by regulators or the private sector. While ensuring the protection of data concerning both clinical trials and healthy volunteers, these systems must be designed to enable participant identification, so that exclusion can be respected during the trial, as well as wash-out periods between trials.

Article 5. Informed consent. Informed consent materials and processes should be adapted to the specificities of healthy volunteers in terms of age, education level, social circumstances, and other potential situations of vulnerability*. Complete information on the research objectives, the study demands and its risks and benefits for volunteers should be presented in a fair way using simple and concise language. A specific focus should be placed on addressing risks of over-volunteering.

Article 6. Sharing trial results with healthy volunteers. After the trial is completed, healthy volunteers should be informed about key aggregated trial results in a fair and understandable way, through appropriate means e.g. written communication or invitation to an in-person meeting.

Article 7. Conflict reporting and management. Processes should be set up for healthy volunteers to report any concern to the clinical site staff, during and after the clinical trial with no risk of prejudice. In addition, processes for reporting issues to a neutral person (e.g. ombudsman) or body (e.g. ethics review board) in a way that ensures confidentiality of the person's identity should be set up. These processes should be detailed in the informed consent documents. Written records should be kept of reported issues and of the actions taken.

Article 8. Research ethics oversight. Ethics review boards involved in assessing healthy volunteer trials should have the skills, training, and capacity to review such trials. Members should understand the risks specific to healthy volunteer trials and how to minimise them.

Article 9. Site and investigator oversight. There should be local oversight systems to ensure that sites conducting clinical trials are appropriately resourced, with staff appropriately trained to ensure the quality of the science and the protection of healthy volunteers. This system should be maintained under a mandatory regulatory process that includes inspection of research facilities, and review of staff credentials.

PROTECTING FROM RISKS OF HARM

The healthy status of volunteers before participating in a clinical trial makes their risk/benefit ratio different from that of patients involved as research subjects in clinical trials. Healthy volunteers may be at risk of bodily harm from specific trial procedures but also from over-volunteering. In addition to physical risks, psychological risks should be addressed.

Article 10. Protection from physical harm. Risks to healthy volunteers should be minimised through the design of the clinical trials which should include only medical procedures that are scientifically necessary for the research questions. Access to acute medical care should be provided throughout the trial.

Article 11. Protection from psychological harm. Research clinics should address the potential for psychological harm that results from strict trial conditions, especially clinic confinement (such as by providing access to telephones, Wi-Fi), and may be exacerbated for participants in situations of vulnerability. Facilities should have sufficient space to properly accommodate participants and be designed to maximise the safety and well-being of the trial participants. Medical staff must remain attentive to participants' needs and provide them with appropriate support and resources.

Article 12. Monitoring of potential long-term harms. There should be a post-trial system of follow up to ensure long-term monitoring of adverse events and healthcare for healthy volunteers. This system should ensure all adverse events that occurred during the trial have been recorded and resolved as well as collect data on any additional adverse events that may develop post-trial.

Article 13. Insurance for research-related injury: There should be requirements that sponsors and/or research clinics have insurance to cover all harms caused by clinical trial participation, including post-trial care for injuries related with the clinical trial.

PROTECTING FROM RISKS OF EXPLOITATION

Healthy volunteers participate in clinical trials without the possibility of direct benefit for their own health. The expectation of receiving financial compensation is often a key motivation to participate and leaving them particularly exposed to the risk of exploitation when they are in situations of vulnerability. Exploitation can take many forms such as when clinics take unfair advantage for healthy volunteers need for income due to their social disadvantage.

Article 14. Attend to potential situations of exploitation. All clinical trial stakeholders should attend to the large variety of potential situations of exploitation that are of special relevance to healthy volunteers. They should be educated on ways to identify collective and individual healthy volunteers' circumstances that may expose them to risks of exploitation and to ensure that steps are taken to address these risks.

Article 15. Financial compensation. Compensating healthy volunteers for trial participation has the potential to compromise trial results by inducing concealment of health conditions and adverse events, as well as over-volunteering to earn more income. Financial compensation should be reflective of the demands associated with each trial and approved by local ethics review boards. Countries should develop guidelines on compensation to provide fair and equitable compensation across research fields. Trial information and informed consent documents should include explicit information on how payments will be made, including provisions that will apply in case of early withdrawal from the trial.

Article 16. Well-being during the clinical trial. Specific attention should be paid to ensuring the well-being of volunteers during the trial. Clinical trial sites should identify and train staff members in charge of ensuring that healthy volunteers are treated respectfully, and their well-being is ensured throughout the research process. Clinical trial information and informed consent documents should include information on how to confidentially report, within and outside the study staff, issues related with well-being.

TOWARDS RESPECTING, REDUCING, REFINING AND REPLACING HEALTHY VOLUNTEERS (4Rs)

Due to the risks to which healthy volunteers are exposed, the promotion of a 4Rs principle [Respect, Reduce, Refine, Replace] should serve as a foundational guide for safe, ethical, and reliable clinical research. Respecting concerns an individual fundamental right. Reducing implies minimizing the number of healthy volunteers exposed to potential risks. Refining impacts the methodologies used to enhance precision and reduce unnecessary burdens and risks on participants. The principle of Replacement advocates for the use of alternative methods when possible. Integrating 4Rs requires a multifaceted approach that encompasses ethical considerations, study design, participant welfare, integrating diverse data sources, leveraging emerging digital technologies and collaboration among different stakeholders.

Article 17. All stakeholders should carefully consider the application of the 4Rs principles —Respect, Reduce, Refine, and Replace in all clinical research stages involving healthy volunteers.

GLOSSARY

Clinical Trial Clinical trials are studies intended to discover or verify the effects of one or more investigational medicinal products in human participants.

Healthy volunteers are human trial participants, who:

- Accept to participate in an interventional clinical trial with no expectation of an immediate benefit for their health,
- Are presumed to be healthy based on tests performed for this specific clinical trial.

Medicinal products include pharmaceutical and biological products tested in clinical trials, as well as pathogens used in controlled human infection models.

Situations of vulnerability include circumstances which compromise the healthy volunteer's autonomy to freely decide to participate in a clinical trial, such as: economic/financial vulnerability, age, limited health literacy, lack of access to healthcare, language barriers, power imbalances, hierarchical relationships, societal or familial pressures, ethnic or cultural vulnerability, unemployment or underemployment, uncertain legal status, etc.

Stakeholders: Key clinical trials stakeholders include healthy volunteers, investigators and their staff, lawmakers, regulators, study sponsors, Contract Research Organisations, policy makers, communities, media, and ethics review bodies.