VolREthics initiative

DRAFT - Global Ethics Charter for the Protection of

Healthy Volunteers in Clinical Trials

Comments document

Please provide comments using the template below and return by e-mail to hvworkshop.disc@inserm.fr by March 30, 2024

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Comments provided by	
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General comments on the draft Charter
The MRCT Center fully supports robust and comprehensive review of a study's design by a research ethics committee in advance of initiation of the trial. Ethics Committee is essential to assess both scientific rationale, study design, and ethical soundness. We thus offer our commentary in support of the. Charter. We appreciate the opportunity to comment on the work to date. Generally, we find it difficult to identify unmet needs of this charter– especially in light of long-standing ethical guidance, e.g. The Declaration of Helsinki, that includes protections for healthy volunteers. Of note, the issue of over-volunteering appears to be a central concern of the Charter and appears to it from other documents. However, neither the charter itself nor the preamble includes any indication of the magnitude of the current problem currently. Moreover, while the preamble indicates that the charter is intended explicitly for regulators, the guidance spans a broader audience and it is difficult to identify where recommendations for regulators are presented.

The MRCT Center recommends that any interventional clinical trial that involves healthy volunteers be required to undergo ethical review and approval by a constituted ethics committee, regardless of other regulatory requirements. There are geographies where studies involving healthy volunteers would not be required to be reviewed. This potential gap should be addressed by an affirmative requirement for review, particularly as this Charter represents a global document.

Comments on specific Charter articles **Please provide comments on the most salient issues you identify.** **To facilitate the process of comments review, please consider focusing on no more than 3 top priorities.**			
Section 1: Valuing the difference: general recommendations			
Article Number	**Text**	**Your proposed reworded text**	**Your comments/suggestions**
1	**Laws and regulations to protect healthy volunteers.** Countries should develop laws and 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.	**Laws and regulations to protect healthy volunteers.** Countries should develop laws and regulations specifically intended to protect healthy volunteers. These should address the risks of harm and of exploitation, promote healthy volunteers' wellbeing in clinical research, and mitigate any potential immediate or long-term negative financial, legal, or cultural, or other (e.g., insurability) impacts of participation.	We recognize the tension between protecting the rights of potentially vulnerable healthy study participants and the scientific rationale for their inclusion in trials, and we fully support the spirit of Article 1. Insofar as Article 1 encourages attention to the regulatory and/or legislative landscape, we recognize that certain legal or regulatory provisions exist that jeopardize the well-being of healthy volunteers. For example, compensation for trial participation may disqualify a person from means-tested program eligibility, or personal medical information may limit future insurability. The harm to which trial are exposed should be limited to potential effects of the investigational medical product itself.

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 and 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 for the duration of the clinical trial, and after in the event of adverse events.		The term "ethics dumping" may be a term of art, but it is not one that is understood internationally. We suggest that the Charter use terms that are understood universally. What do you mean by the term?
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.	**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, to clarify that participation in research does not provide access to routine health care, and to emphasize that participation is voluntary.	We worry that vulnerable populations may conflate participation in a clinical trial with access to routine health care. We feel that recruitment practices should ensure the difference between research and care is clear.
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,	**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 an independent, unconflicted representative of the private sector. While ensuring the	We believe the suggestion here for a national or regional system to prevent over-volunteering holds merit, but any responsible private sector entity must be independent and free from any financial or other conflict of interest. Further, the necessity of unique participant identifiers that are shared across geographical boundaries should be explicit, and complementary to privacy protections for the individual volunteer.

	so that exclusion can be respected during the trial, as well as wash-out periods between trials.	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, wash-out periods between trials, and across geographic boundaries.	
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 the about risks of over-volunteering.	**Informed consent.** Informed consent materials and processes should be adapted to the specificities of 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 and understandable way using simple and concise language. A specific focus should be the about risks of over-volunteering. *To what does this refer?	We offer full support for the need for clear communication throughout the informed consent process, but we note that this expectation extends beyond "healthy volunteers." We believe informed consent for all trial participants "should be adapted to the specificities of [all] volunteers in terms of age, education level, and other potential situations of vulnerability." Also, there is no footnote associated with the asterisk that we could identify. To what is this asterisk intended to draw our attention?
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.		We agree that providing key aggregated trial results will honor healthy volunteers and increase trust and transparency between sponsors and participants. We do, however, question the intended meaning of the word "fair" in this context and feel that more information on this point be included or that the word be deleted.
7	**Conflict reporting and management.** Processes should be set up for healthy volunteers to report any		No comments.

	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 protocol and the informed consent documents. Written records should be kept of reported issues and of the actions taken.		
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.	**Research ethics oversight**. Ethics review boards involved in assessing healthy volunteer trials should have the skills, training, and capacity to review such trials and be free of conflicts of interests with the research. Members should understand the risks specific to healthy volunteer trials and how to minimise them.	This section would benefit from the explicit mention that conflicts of interest among ethics oversight boards be managed or eliminated.
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.		Remote oversight is now routine. Specific mention of the expectation that remote monitoring will be enable and that onsite monitoring and inspection are sometimes required would be beneficial. Further, the settings in which onsite monitoring are necessary should be explained.
Section 2: PROTECTING FROM RISKS OF HARM			
Article Number	**Text**	**Your proposed reworded text**	**Your comments/suggestions**
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		See general comments: Explicit inclusion of the requirements for review and approval by a research ethics review board should be mentioned.

	research questions. Access to acute medical care should be provided throughout the trial.		
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 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.	**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 accommodate participants and be designed to maximise the safety and well-being of the trial participants. Whenever strict trial conditions are warranted by the study question and its outcomes and/or outweighed by the potential benefits of the research, justification should be given, and explicit research ethics review provided. Medical staff must remain attentive to participants' needs and provide them with appropriate support and resources.	We worry here about the absence of consideration given to possible exceptions to these requirements (e.g., a sleep deprivation study). We suggest the addition of the sentence "Whenever "strict trial conditions" are warranted by the study question and its outcomes and/or outweighed by the potential benefits of the research, justification should be given, and explicit research ethics review provided.
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.		Adverse events, broadly defined, are routinely identified, and recorded during a clinical trial. However, after the trial participant's trial termination, regular monitoring by specialized trial staff is burdensome and potential unwelcome. We worry about the breadth and scope of the recommendations in this article and the lack of any time boundary to this expectation. An expectation of a causality assessment should be included.
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.		
Section 3: PROTECTING FROM RISKS OF EXPLOITATION			
Article Number	**Text**	**Your proposed reworded text**	**Your comments/suggestions**
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 14 appears to articulate the motivation behind the construction of this charter, but it does not seem to provide any new actionable guidance or insight. Further, if an ethics review board is credible and has approved the protocol after evaluation of the risks and benefits *in the absence of* consideration of financial considerations, then the provision of financial or other benefits cannot be exploitative.
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.	Suggest modification of the fourth sentence: … Trial information and informed consent documents should include explicit information on how payments will be made, the provisions that will apply in case of early withdrawal from the trial, any risks to means-tested program entitlements, or taxation consequences of such payments.	We appreciate the value in implementation of clear communication standards for how payments will be made during the informed consent process. We also recommend that mention of the risks of payments (e.g., taxable income, risks to means-tested entitlements) be mentioned.

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.		
Section 4: TOWARDS RESPECTING, REDUCING, REFINING AND REPLACING HEALTHY VOLUNTEERS			
Article Number	**Draft text**	**Your proposed reworded text**	**Your comments/suggestions**
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.		
Please tell us below which of the above 17 articles are most relevant to your organization. Thank you for your comments.			