



VolREthics initiative

Results of the public consultation of the Draft “Global Ethics Charter for the Protection of Healthy Volunteers in Clinical Trials” February 21, 2024 version.

NOTE: Comments were received from 43 persons and institutions. Only the names and comments of the 36 persons who have explicitly accepted their publication are shown here. Some comments which were very identical in nature have occasionally been merged.

Comments received from the following persons and institutions:

Persons:

- Alaa A. Youssef Abouelfetouh
- Love Ankrah
- David Appiah
- Frédéric Arenou
- Varvara Baroutsou

Comments made on behalf of institutions:

- Tanya Coetzee on behalf of Members of SAMAREC (South Africa)
- David R. Curry on behalf of members of the GFREI (Global Forum for Research Ethics and Integrity)
- Jake Eberts on behalf of 1Day Sooner
- Yasmin Nagaty on behalf of The Middle East Association of Pharmaceutical Medicine Professionals CIO (MEAPP)

- Helen Busby
- Primus Che Chi
- Onyinye Chime
- Kyle Conner
- Shereen Cox
- Tam Dong Thi Hoai
- Farbizio De Ponti
- François Eisinger
- My Elhassan Elkarimi
- Antonie Fuhr
- Namita Ghimire
- Delphine Grison
- Lehua Gray
- E Li Leong
- Nandini Kumar
- Chieko Kurihara
- Sucheta Banerjee Kurundkar
- Yasmin Nagaty
- Fredrick Omiti Ochuodho
- Mercury Shitindo
- Keller Scholl
- Doris Schroeder
- Craig Tipple
- Olinda Timms
- Rebecca Walker
- Dave Wendler

- Christophe Rouquette on behalf of Groupe inter-associatif TRT-5 CHV

General comments

Is any major issue not addressed?

Inclusion of specific guidelines for handling unforeseen conflicts of interest among stakeholders involved in clinical trials.

Is its target audience(s) clear and relevant?

Consider adapting to general public to foster greater transparency and accountability.

Is it easy to understand?

Try simplifying complex terminology and concepts and expanding the glossary

The Charter is quite 'bland' and unspecific/too general

It is also inconsistently structured. Bad practice and negative aspects should not be first.

The document should address, in that order, good practice, education and training to ensure good practice, prevention of malpractice and sanctions if there is malpractice. For example there is far too much emphasis on over-volunteering. Fair compensation should come first and then second the risk over-volunteering, as this is not the only risk. What happens if a centre does not comply with good practices/regulations ? Shouldn't they be barred from performing such trials?

Major issues not addressed

- reference to international ethics standards for the laws and regulations.
- The 4 Rs have become a few words, quite unspecific (e.g. on refine).
- A good balance in the wording between obtaining good representation of the drug target population and non-exploitation of vulnerable participants - some of whom might be the target population.

There is no such thing as benefit/risk RATIO. This is not numerical but a **balance** and a scientific assessment.

Reword introduction to "valuing the difference" into :

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) risks of being exploited when the agreement to participate is based primarily on financial incentives ; and
- (iii) the constrained research settings and conditions required by the clinical trials.

Suggest replacing 'should' with 'must' throughout.

I was surprised that the main target audience is political authorities with the aim of developing local laws and regulations. Another or complementary way would be to put more clearly the responsibility on sponsors and their reporting obligations (towards financial markets, drug registration authorities, etc.) which would also lower the risk of ethics dumping (similar to what companies address in sustainable procurement for example).

In low and middle income countries, there is a greater possibility of exploitation and over-volunteering for financial gain. The charter could propose education of the general population on research. Every research facility should have some funds allotted for regular research volunteering to the general public, online and offline, including town halls before the start of recruitment

The recommendations focus on risks, which are obviously important. I think it would also be valuable to discuss the social value of the studies in question. As the text notes, many HV enroll to make money. But, data find that many also hope to help others. That requires studies with social value. I have argued that avoiding exploitation also requires assessment of the benefits, especially when a study is sponsored by a for profit company. Reducing compensation to participants may increase rather than decrease exploitation: doi: 10.1353/pbm.2020.0023. Finally, many groups now emphasize the social value of participation in research, such as 1 days sooner. Including this would ensure that these recommendations remain timely.

Compensating can increase "process" exploitation, which I think is the worry here. But, it can also decrease "outcome" exploitation. This is an increasing worry as more studies are sponsored by for profit entities. Should this include something about worries of companies making lots of profits off the efforts of HVs?

Is its format appropriate? I think the general recommendations (section 1) could be organised in terms of themes: 1) Advocacy & Education, 2) Governance (legal & ethical), 3) Best Practices, 4) Redress

Could we cite countries which have specific laws ?

I would pitch five principles, based on both my academic research and my lived experience as a volunteer, covering some but not all of your 17 articles.

1. **Adequate information.** Consent documents should not only include medical risks, but focus on the practical impacts: days in confinement, number and flexibility of follow-up visits. Regulators and researchers should establish and use a system for tracking patients across studies to prevent over-volunteering, cross-check medical information to avoid the concealment of conditions, and have appropriate disclosure requirements in volunteer contracts to enable this.
2. **Adequate benefit.** Medical harm should be at the minimum level necessary for good science and reasonable costs.
3. **Adequate care.** To the extent practicable, patients should have access to entertainment, socialization, exercise, medical treatment both during and after the study,
4. **Adequate representation:** ethics review boards should have representatives from the socioeconomic status, income, and other factors of marginalization that their orgs recruit from, possibly including bringing in members of outside groups on a temporary basis when dealing with new recruitment populations. Anyone who thinks it is unethical to pay poor people too much money (not them, they should be paid their six-figure salary, of course) should have to look in the eye someone who has struggled to make rent as they say so, and be embarrassed if the study is then unable to recruit enough participants because of inadequate compensation.
5. **Adequate compensation.** Trial participants should be paid well for their service to humanity, taking into account the risks that they take and the difficulties involved.

Replace "adverse events" by "adverse consequences"

Creating a space for global harmonisation and inclusion of this Charter in all relevant authorities and stakeholders involved in clinical research, Enhancing capacities of IRB | IEC to seamlessly incorporate the charter in their day to day scope of mandate

The charter is very relevant and addressed major issues, the format is good and target audience is clear and relevant. Yet, this charter may be technical to a layperson. Also, this article may have ignored the needfulness of **community/group engagement in recruitment of participants**. This should be added.

Overall, the Global Ethics Charter seeks to uphold the principles of respect for persons, beneficence, and justice in the conduct of clinical research involving healthy volunteers.

We hope all stake holders will adhere to these ethical guidelines, to promote trust, integrity, and the well-being of all individuals involved in clinical trials.

Article 9 could have the most impact on our organization, however most impactful from our organization point of view are the aspects mentioned in the general comments, the article 4 (when considering clinical trials conducted in third countries used for to support marketing authorizations within EU).

The charter is generally easy to understand and provides valuable guidance for stakeholders and researchers in developing the country's roadmap for clinical trials involving healthy volunteers.

Article 4 is pertinent to the Ministry of Health Malaysia due to the existing platform that enables cross-checking of all healthy volunteer data before enrollment, effectively preventing instances of over-volunteering.

The following comments were sent out to the undersigned former human research participants in early phase vaccine or drug studies and/or human challenge/controlled human infection studies, and some feedback has been incorporated. Each of the people below endorsed the attached comments, which were sent out in final form three days before submission...

The vast majority of articles in this draft are relevant to 1Day Sooner, given our focus on representing the interests of volunteers in some of the more ethically complex studies involving healthy participants, namely, those related to infectious disease research, including human challenge trials. **Article 2 is perhaps the most highly relevant** to 1Day Sooner, as it describes support for the formation of associations that would be very similar to the model we have attempted to pioneer.

This charter is an extremely important, valuable document, especially as it is "primarily intended for policy makers". This is because, as noted in the document, "very few countries have special legal provisions addressing the risks that healthy volunteers may face". However, some parts of the document are too general, ambiguous, without providing practicable suggestions specific to healthy volunteer studies. Regarding this point, we will comment to each individual item.

As the general comment, preamble should be reconsidered from the following points:

1. Specific examples of healthy volunteers who are particularly at risk of exploitation need to be given. For example, the needy, prisoners, those in the lower classes of hierarchical organizations, people in LMICs participating in clinical trials of sponsored by global companies, etc.
2. There is a statement that "these studies are usually conducted in dedicated facilities with strict rules" but it is necessary to caution that these studies are also conducted in universities and research institutions (including non-medical institutions) without strict rules or even without oversight of medically qualified staff.
3. Pharmaceutical companies should be included in the main stakeholders mentioned that "ethics committees, research organisations, regulators, health professionals, and healthy volunteers".
4. The following should be considered as missing points of this document:

- There is no mention about secondary use of data. Not specific to HV
- No mention about withdrawal rights.
- Many articles state that countries should do.... without specifying or proposing which authority or body.
- The preamble states that healthy volunteers do not expect direct benefit, however they get full health check-up free of charge.
- Also in the preamble, it's mentioned that the risk-benefit ratios for healthy volunteers are completely different from that of patients, however this is not entirely true as in placebo controlled randomised trials half of the patient get placebo.
- In the preamble, bioequivalence studies should be listed among studies that involve healthy volunteers.
- Some medical devices require clinical trials in healthy volunteers, not only medicinal products.
- Risk/benefit ratio is better replaced with risk /benefit assessment throughout the document as we don't have mathematical numbers.

Also, order of articles should be reconstructed according to the proposed legal system and then practicable aspects in the order of plan and conduct of a study.

Article 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.
Comments
Countries should develop laws and regulations specifically intended to protect healthy volunteers in line with international ethics standards. These should address the benefits of HV trials, promote the HV well-being as well as prevent the risks of harm and of exploitation, especially through education and training.
We are writing trials and research. Can we use a single terminology? Trials and research aren’t the same, hence my query. Trials according to me are a part of clinical research. Please correct me if I am wrong.
Countries should develop laws and regulations that <i>are globally acceptable in line with the global Charter</i> specifically intended to protect Healthy Volunteers. These should address the risk of harm and exploitation, as well as promote healthy volunteers’ wellbeing in clinical research
Are we looking at Universal laws or country tailored laws?
Specific standards for vulnerable subjects need to be defined. It would be appropriate to define two categories of vulnerable subjects. The first, which must be formally excluded from healthy volunteers, includes the elderly, prisoners, major disabilities and pregnant women. The second category, whose recruitment must be strictly limited, such as imposing a quota, includes people in economic distress, people of color, ethnic minorities and immigrants.
The title “Valuing the difference” is confusing or misleading. We recommend changing to “General recommendations to protect healthy volunteers and ensure their well-being”.
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. 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?
Proposed revised wording: 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.

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 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.

Comments

1. Countries should support the formation of groups **or associations** of past and present healthy volunteers...
2. Interactions with associations representing healthy volunteers should be facilitated **by the government** to fight double standards, avoid ethics dumping....

Laws and regulations governing clinical research should explicitly mandate the establishment of representative groups/associations for healthy volunteers. These groups, comprised of past and present participants, will serve as **critical stakeholders** throughout the research ecosystem, actively shaping and safeguarding their interests.

What do we mean by 'closure'. I suspect results dissemination? In which case, should we be more specific on that?
Not familiar with term 'ethics dumping'
I wouldn't use 'adverse event' since it could be unrelated to the intervention.

The ideas of fighting double standards and ethics dumping in the original text are not defined and I suggest dropping. I suggest instead adding the term "equitable" to the first sentence. I also think that the recommendation for medical care for adverse events is not adequately related to the idea that healthy volunteers be included in the *development of standards* and so should not be part of this article but should be included elsewhere in the charter.

Not easy as motivation of healthy volunteers to organize themselves could be low. I would rather encourage discussion with representatives from disenfranchised communities and patients associations of chronic diseases for example (a healthy volunteer for given medicine might have other health issues and be more at risk than general population). So the first step would be to research who are volunteers and those most at risk.

Recommending actions for Sustainability of representatives groups would be necessary under this article or could be addressed in a separate article.
I strongly support formation of a group of past and present healthy volunteers to represent our interests. In my experience the normal ethics review and oversight typical at US research organizations was more than adequate from an strictly ethical perspective, but it would have been nice to have voices of past volunteers to identify things which aren't technically ethical problems (ex. all the pre-prepared meals were terrible; spotty internet during our 4 day quarantine stuck in our rooms meant we all were terribly bored) but are impact quality-of-life during a trial. Those are things that past or present healthy volunteer would have the perspective to advocate for.

In the presence of strong regulation, the contribution of associative work would be unnecessary.

There is a risk that those "ASSOCIATIONS" become the exploiters and be like employment agencies.
It should be voluntary not for profit and measures should be in place to ensure non-exploitation of volunteers.
There is also a risk of breach of privacy of participants and it is a bit strange to facilitate only associations of healthy volunteers without background reasoning of general need for associations of research participants, not limited to healthy volunteers.

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?

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.

Comments

Maybe we could add here: Countries should support efforts to involve hard-to-reach groups of potential participants (e.g. women with children, people from rural regions) to increase the representativeness of the group of HVs.

What does the misleading language relate to? It might be helpful to spell that out.

The last sentence could include a broader suggestion as regards diversity and inclusivity. (Not expert enough though to assess whether this is appropriate.)

Think need to be clear on this.

Suggest give examples of populations considered as disenfranchised.

I prefer the term vulnerable over the disenfranchised

I feel misleading language is not wide enough

“Countries should develop frameworks to ensure that recruitment practices adhere to ethical standards that prevent excessive emphasis on financial compensation and other forms of influences. Specific attention should be paid to prevent targeting vulnerable populations.”

This article may have ignored the needfulness of community/group engagement in recruitment of participants. This could be addressed as a separate article.

I suggest adding language to support the equitable representation of different groups relative to expected risks and benefits

Specific standards for vulnerable subjects need to be defined. It would be appropriate to define two categories of vulnerable subjects. The first, which must be formally excluded from healthy volunteers, includes the elderly, prisoners, major disabilities and pregnant women. The second category, whose recruitment must be strictly limited, such as imposing a quota, includes people in economic distress, people of color, ethnic minorities and immigrants.

Please consider adding that the system should be comprehensive, for example: “There should be a mandatory, **comprehensive** system in place in all contexts of clinical research to prevent over-volunteering...”

Some countries (e.g. India) have several privately held registries in use already, but the challenge is that the registries do not communicate with each other and therefore, they do not really help to identify over-volunteering.

The system should be promoted nationally and, if feasible, should be included as a mandatory item in the study protocol. This would require researchers to regularly update the database and simultaneously verify the status of all healthy volunteers before enrolling them, ensuring prevention of over-volunteering.

Recruitment strategies should be broad-based to include diverse genders and participants. However, current participation patterns often disproportionately enrol fairly young, male, economically disadvantaged or unemployed individuals and people of colour. Current practices indicate selection bias with serial participants and reduced external validity. Addressing this imbalance is crucial. Consequently, we have overrepresentation of individuals who are not representative and in the case of serial participants who are less susceptible to adverse events, drug safety data are seriously impacted and lack external validity.

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.

Proposed revised wording : 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.

In addition, information must be shared to contact the study staff with any events or concerns in the period to follow after the administration of the medicine and for a period as indicated in the Informed Consent

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.

Comments

Over volunteering is overemphasised in the whole Code.

Unclear statement: “exclusion can be respected during the trial”

What is meant by ‘all contexts of clinical research’?

Private sector management for a mandatory system? If managed by the private sector, should have state oversight.

Think ‘washout period’ needs a definition in the glossary.

A compulsory framework should be established across all clinical research settings to deter over-volunteering, such as simultaneous enrollment in multiple trials or neglecting the necessary "washout" period between studies, regardless of geographical borders. Depending on national or regional factors, this framework could be overseen by regulatory bodies or private entities. It is essential that these systems prioritize the protection of data pertaining to both clinical trials and healthy volunteers. Furthermore, they should be structured to facilitate participant identification, allowing for appropriate exclusions during trials and observance of washout periods between studies.

Perhaps this could be “ensuring/adherence to wash-out periods between trials” instead of preventing over-volunteering.

Reason: How does one define over-volunteering? Is the reason really over-volunteering or possibility of harm to habitual volunteers who fail to adhere to wash out periods

How would this be accomplished? Would it be through a registry or self-declaration?

Emphasis should be both on the protection of the individual and quality of scientific results as a public health good.

There are a few elements that could be expanded or clarified:

1. **Enforcement mechanisms:** It mentions the need for a mandatory system but doesn't elaborate on how this system would be enforced or regulated. Are there penalties for non-compliance, and who oversees the enforcement?
2. **International cooperation:** While it mentions prevention across national borders, it might benefit from emphasizing the importance of international cooperation and standardization to ensure consistency in preventing over-volunteering globally.
3. **Participant education:** It could be valuable to include a brief mention of participant education and awareness programs to help volunteers understand the importance of observing required washout periods and the risks associated with over-volunteering.
4. **Ethical considerations:** While it mentions the protection of data and respect for exclusion criteria and washout periods, it could explicitly highlight the ethical considerations underlying these measures, such as safeguarding participant well-being and maintaining the integrity of clinical trial results.
5. **Data privacy/protection:** It briefly touches on data privacy and protection by mentioning the need to ensure the protection of data concerning both clinical trials and healthy volunteers. However, it could benefit from further elaboration on specific measures or protocols that would be implemented to safeguard participant data privacy and ensure compliance with relevant data protection regulations. For instance, the paragraph could include language about the anonymization or pseudonymization of participant data to minimize the risk of identification. Additionally, it could discuss the implementation of secure data storage and transfer protocols to prevent unauthorized access or breaches. Furthermore, it might be useful to mention the importance of obtaining informed consent from participants regarding the collection, use, and storage of their data and ensuring transparency about how their data will be handled throughout the clinical trial process.

Healthy volunteers should be made aware of wash out period and limited participation during the period, what constitute the washout period.

Highly relevant

There should be a mandatory *centralised identity database* in place in all contexts of clinical research to prevent over-volunteering

There should be a mandatory system of registration of trial participants in place in all contexts of clinical research to prevent over-volunteering....

The registration system will reveal the gender diversity on top of serial participants, so that the safe use of pharmaceuticals from phase I will have a higher external validity It is extremely important to “mandatory” system to prevent over-volunteering. Just stating “system” is not enough. It should be “system of registration” of individual volunteer.

For example, in Japan there is such system organized by an association of research sites, however, this system is not legally-defined mandatory system, thus, there are many commercial organizations which inappropriately induce volunteers, disseminating information through internet “how to escape from the trap of registration system”. Stating the need for “mandatory registration system” is very important.

What is the incentive for private sector?

Measures should be in place to avoid volunteers’ exploitation.

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.

Proposed revised wording : 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 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.

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 the about risks of over-volunteering.
Comments
Informed Consent: Informed consent materials and processes must be tailored to accommodate the unique characteristics of healthy volunteers, including considerations such as age, education level, social circumstances, and potential vulnerabilities, ensuring thorough comprehension. Comprehensive information regarding the research objectives, study requirements, and associated risks and benefits should be presented in a clear, unbiased manner using language that is straightforward and concise, preferably in the participant's preferred language if feasible. Emphasis should be placed on mitigating risks associated with over-volunteering. Moreover, volunteers should be afforded ample opportunity to pose questions and seek clarification before providing consent, thereby promoting informed decision-making and ensuring participant autonomy.
Delete "A specific focus should be the about risks of over-volunteering". Addressed elsewhere
You probably want to exclude children anyway, don't you? Or mostly. So it is unclear why 'age' is mentioned here. Old age? Also, how would researchers do this? Check education levels in the recruitment process? This might be seen as quite intrusive.
The possibility to withdraw at any time without penalty should be clearly indicated in the informed consent. Medical follow up should be offered after withdrawal to make sure withdrawal is not linked with severe adverse event Specific focus on personal data handling and confidentiality should be added
Informed consent procedures and materials must be tailored to the unique characteristics of healthy volunteers, including factors such as age, educational background, social context, and any potential vulnerabilities they may face. Clear and comprehensive information about the research objectives, study requirements, and associated risks and benefits should be provided in a transparent and easily understandable manner. Special attention should be given to educating volunteers about the risks associated with over-participation.
This seems mostly focused on initial consent. Might be valuable to also address importance of on-going consent
Perhaps non-technical jargon could replace the word simple as simple is subjective. NB: See comment re #4- is the issues over-volunteering or risk of non-adherence to wash-out periods?
A specific focus should be about the risks of over-volunteering.
As risks of over-volunteering would by necessity be highly specific to the trials in which individual is participating, we suggest including a recommendation in the charter that standard language should be developed that can be added to any consent form.
It should be stated that there will be separate informed consent documents for healthy volunteers and other participants; adapted to their specificities.
For example, CTR 536/2014 Article 29 5§ states that it should be verified that the subject has understood the information. Something similar could be useful.
In developing countries, the problem of language is acutely present in the preparation of information and informed consent materials. A mention of local languages must be included in the charter. A standard model of the Information and Consent Note can be drawn up and made available as an appendix to the Charter.

Request in an additional article between the 4th and 5th that social circumstances and other potential situations of vulnerability be listed and defined in the legislation/regulations to leave as little room for personal appreciation as possible by the project team.

The issues addressed in this article should apply to all informed consent documents, whether volunteers are healthy or not. Inclusion of details about age, education level, etc., may inadvertently suggest these considerations only apply to healthy volunteers. Consider clarifying this or limiting information in this article to those issues unique to consent for healthy volunteers. Also consider avoiding passive voice in order to clarify who is responsible for the consent process. Because over-volunteering may not be a consideration in all circumstances, we also recommend indicating “as applicable” or “when relevant” in the language of this article.

Proposed wording: Investigators should adapt Informed consent materials and processes to the specificities of healthy volunteers as appropriate, such as by including information about the risks of over-volunteering and of not observing recommended washout periods. When relevant, specific focus should be given to the risks of over-volunteering in the consent process.

Voluntary withdrawal at any time without any penalties (e.g being blacklisted for future recruitment) should be highlighted.

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?

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.

Comments

In case that the trial is not completely finished, but due to urgent health issue, does the participant have the right to know in which arm (study product or placebo) he/she was or not?

After the trial is completed, healthy volunteers should be **provided with** key aggregated trial results fairly and understandably, through appropriate means e.g. written communication or invitation to an in-person meeting **depending on their preferences and the study's nature.**

Incidental findings should be covered. E.g. a brain scan in the trial looking to establish normal function which detects a tumour.

Keep in mind that even if it is a legal provision in France, it is not complied with.

Upon completion of the trial, it is essential to promptly inform healthy volunteers about significant aggregated trial findings in a fair and comprehensible manner. This communication should be conveyed through suitable channels, such as written correspondence or invitations to in-person meetings.

Healthy volunteers should be given a chance to say whether they would like the trial results to be shared with them or not, during, and after the study. If they agree, then during and after the trial is completed, healthy volunteers should be informed about key aggregated trial results in a fair, easy and understandable (lay man's language) way, through appropriate means e.g. written communication or invitation to an in-person meeting.

Normal people don't go to in-person unpaid meetings about the results of the trial. A one-hour meeting probably entails at least an hour of travel, at no personal benefit.

I suggest healthy volunteers should be given options to choose to either receive feedback of trial results or not.

For the trial I participated in, multiple people had flown across the country to be participants. Asking them to return for an in-person meeting as the only way to access results would involve unreasonable expense and difficulty, and would mean these people couldn't get access. I support 1DaySooner's request to specifically request written communication about study results at a minimum.

The requirement to publish results in CTIS-portal is already implemented in CTR 536/2014. This could be notified in context with Europe. In addition to disseminating the trial outcomes after the trial is completed, I would like to propose sharing any adverse event discoveries (both short-term and long-term) to inform healthy volunteers and encourage them to monitor their health status going forward. For studies with multiple arms and blinding procedures, it would be beneficial to disclose the arm allocation to healthy volunteers, allowing them to remain vigilant for potential long-term side effects. Proposal to share any findings of adverse events (short and long term) to inform healthy volunteers and encourage them to monitor their health in the future.

Meetings require that participant's schedules allow for them to attend. Recordings of meetings may also require that a participant devote substantial time to listening for key information. While meetings or presentations can be helpful and good, we recommend they only be used in addition to written communications, not as substitutes. While meetings or presentations can be helpful and good, we recommend they only be used in addition to written communications, not as substitutes.

Provide for communication during the trial outside of cases of reports or conflicts (information on the progress of the trial, interim results, etc.);

After Article 6, an additional article should be included on the rights and remedies available to healthy volunteers, in terms of access to their data, for example but not only, providing for the provision of appropriate explanations and the provision of appropriate support.

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. Extreme care is needed to avoid unexpected leak of information in the process of contact to volunteer beyond the term of trial at the facility.

Registration of trial information including results in public database is also needed for this end.

It is very important to share trial results with study participants, not limited to the case of healthy volunteers. Especially in case of healthy volunteer, there would be cases where study participants do not share with their family members the information of the fact of participation. For this reason, extreme care is needed to find appropriate way to contact them beyond the term of conducting study at research facility.

It is also necessary to include the requirement of trial registration into public database because ICMJE's requirement of clinical trial registration exclude early phase trials.

There is no requirement at the moment to publish phase 1 results in clinTrial.GOV, this could be the start.

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.

This could be impractical as these results take years to be finalised. The best is to communicate the approval of phase 2 trials to the healthy volunteers who have participated. To ease this administrative burden, it could be requested as part of the informed consent to indicate if they want to receive any communication about further trials or results from these trials.

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 protocol and the informed consent documents. Written records should be kept of reported issues and of the actions taken.

Comments

Address no fear of reprisal / retaliation in a way that ensures confidentiality of the person's identity.

From an English language perspective, 'complaints process' is a more easily understandable term than conflict reporting and management. It is widely used, so familiar.

in a way that ensures protection of the reporter (including confidentiality of the person's identity) should be set up

Procedures must be established to enable healthy volunteers to raise any concerns with clinical site staff both during and after the clinical trial, without fear of reprisal. Additionally, mechanisms should be in place for reporting issues to a neutral party, such as an ombudsman or ethics review board, while ensuring the confidentiality of the volunteer's identity. These procedures should be clearly outlined in the trial protocol and informed consent documents. Detailed written records should be maintained regarding reported concerns and the corresponding actions taken.

Anonymous reporting is best

I suggest adding language that ensures that the kept written reports will respect the confidentiality of the identity of the reporting person.

"Written records should be kept of reported issues and of the actions taken, in a way that ensures the confidentiality of the reporting person's identity".

Please consider adding anonymously: "Processes should be set up for healthy volunteers to report **(if possible, anonymously)** any concern to the clinical site staff, during and after the clinical trial with no risk of prejudice."

Anonymous reporting option could lower the reporting threshold. Even if reporting possibility to a neutral person is recommended, it can still be intimidating.

Suggest replacing heading with “Reporting and management of participant concerns.’

The term ‘conflict’ is provocative and implies an intrinsic set of assumptions about the research endeavour, i.e., that it is a realm in which conflict naturally or frequently arises. In U.S., ‘conflict’ is not a term that is typically used in consent forms, rather participant ‘concerns’ or ‘complaints.’ While the charter is directed at specific stakeholders, the larger stakeholder is the general public, and as was evidenced during the pandemic, public perception plays a key role in the success or failure of public health policy. Using terms like ‘conflict’ have ramifications that may adversely affect public perception towards the clinical trial enterprise as a whole.

This could be taken by regulatory authority and Ethics Committees

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.

Comments

Although the term ‘ethics review board’ is sometimes used, it is more usual in my experience to refer to IRBs (in the US) and RECs (in other contexts).

Research ethics oversight: The country should have a legal provision to form Ethics Review Boards (ERBs) and ERB members with diverse backgrounds and expertise, including individuals with experience in conducting or overseeing trials with healthy volunteers. Members should be equipped with the necessary skills, training, and capacity to effectively assess healthy volunteer trials is essential for maintaining the highest ethical standards in clinical research.

Ethics review boards responsible for evaluating trials involving healthy volunteers should possess the necessary skills, training, and resources to effectively review such studies. Board members should be knowledgeable about the unique risks associated with healthy volunteer trials and adept at devising strategies to mitigate them. Furthermore, they should demonstrate the willingness to halt a trial if it is deemed unsafe for participants.

At least one member of every ethics review board should be someone who has done a healthy volunteer trial before and shares an understanding with other trial volunteers.

Add a point about the availability of appropriate training?

Ethics Review Boards should factor policies to deal with possible conflict of interest

See comment made in general section on “social value”

Training in the bioethical evaluation of trial protocols on healthy volunteers may be offered, possibly under the aegis of the IBC (UNESCO). In the same way, a certification can be offered to validate the training.

From a chronological point of view, it might be appropriate to place Article 8 directly after Article 5, both of which deal with steps prior to the participation of individuals;

(Add following text)

Conflict of interest disclosure of the members of ethics review boards should be required. In addition, ethics oversight should include scrutiny of negative impact of commercialization of academic research facilities.

The case of Gelsinger in US in 1999 and other cases of deaths of volunteers in US raised issue of conflict of interest and competitiveness of academic institutions to get money from companies. Need for oversight of research ethics including COI and commercialization should be cautioned.

Proposing training and certification on a yearly basis.

This section would benefit from the explicit mention that conflicts of interest among ethics oversight boards be managed or eliminated.

Proposed revised wording : 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.

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.

Comments

This system should be maintained under a mandatory regulatory process that includes inspection of research facilities, review of staff credentials, and actions to prevent further trials in the centre if the conditions are not respected.

Local = national?

Are we suggesting something above and beyond GCP here – think need to be clear on that. For me, all sites must meet GCP standards. It's OK to advocate for a standard about that for health participants (I support that) but it may not be relevant to all studies. First in human, for sure, but a BE study or a new formulation?

Local oversight mechanisms should be established to guarantee that clinical trial sites are adequately equipped and staffed with appropriately trained personnel to uphold scientific rigour and safeguard the well-being of healthy volunteers. In cases where delegation is involved, investigators must periodically review all documents to ensure compliance and ethical conduct. This regulatory framework should mandate routine inspections of research facilities and credential reviews of staff to maintain the integrity of the system.

Could also be a requirement to maintain a quality management system and a requirement to officially certify the site / facility.

Clinical trial inspections are well codified. They usually cover all aspects of a trial. The important thing here is to clarify and clarify the aspects of trials on healthy volunteers.

Make participant welfare a top priority.

Implement a system of stronger voice and resource, e.g., a system for reporting and responding to research complaints, with relevant information included in the informed consent form.

Apply high level of transparency and information sharing with involvement of healthy volunteers in providing feedback on policies, practices and clinical trial processes would be beneficial.
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.

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.
Comments
I wouldn't put two very separate things into one article.
Not only medical procedures Do we want to be clearer about the need for acute medical care to be 'rapidly' available (e.g. the ability for patients to be stabilised within the trial facility by an emergency response team). Some sites would argue that a 10 minute wait for an ambulance and subsequent transfer to an acute facility constitutes 'access' – I would argue not.
mention the importance of doing the eligibility screening to identify potential volunteers with underlying conditions that might be aggravated by participation in the trial.
Risks to healthy volunteers should be minimised through risk mitigation in trial design. This entails including only those medical procedures that are scientifically essential for addressing the research questions at hand. The principle of scientific necessity should guide the selection and implementation of procedures throughout the trial protocol. Mechanisms must be established to provide and ensure continuous access to acute medical care throughout the trial. Prior to the commencement of the trial, a thorough risk assessment should be conducted to identify and evaluate potential hazards and adverse events that healthy volunteers may encounter.
Scientifically established low toxicity in models is ideal.
This could also include information of late adverse events, if any. Please notify, that there are already some guidances and these could be mentioned: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-and-mitigate-risks-first-human-and-early-clinical-trials-investigational-medicinal-products-revision-1_en.pdf
(Add following text) For the first-in-human studies and other studies with high-risk, it is necessary to introduce system of certification of facilities, including availability of medically qualified staff with adequate emergency care training.

In addition, recommendations for low-risk invasive study, such as in blood draws only, should be developed. The case of TGN1412 in UK in 2006 raised the need not only for “access to acute medical care” but also need for staff trained in emergency care and for institutional accreditation system in case of first-in-human trials. The case of BIA 10-2472 in 2016 raised the need for stricter oversight not only the case of first-in-human cohort. For this reason, it is required that regulators develop the system of certification of facilities to conduct high risk, early phase studies that includes the availability of medically qualified staff with adequate emergency care training.

On the other hand, stricter rules by EMA may lead to outsourcing of studies to areas of low resource settings. Comment from this view is described for Article 14.

In addition, recommendations for low-risk invasive study, such as in blood draws only, needs to be described.

See general comments: Explicit inclusion of the requirements for review and approval by a research ethics review board should be mentioned.

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 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.

Comments

from strict trial conditions, especially clinic confinement (such as by providing access to telephones, Wi-Fi), or incidental findings, and may be exacerbated

In the second part of the article, this is now about safety, not about psychological harm.

The example of WIFI and telephones reads like they are considered as potential harms. Suggest move those mitigations to the next sentence. Also – think need something here about appropriate consent to the conditions that are necessary...

Maybe broaden even further to include other risks, e.g. social risks.

First sentence is too compounded and not very clear in terms of readability.

It might be good to add here language to ensure protection from psychological harm, including potential stigma resulting from participating in certain trials in certain populations or underclass certain conditions.

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.

Proposed revised wording : 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.

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.

Comments

I don't see how this is workable or needed and suggest it is removed. Sponsors cannot have an indeterminate responsibility and GCP is clear that AE collection stops with the end of the trial.

The length of follow up should be described in the protocol and validated by the IRB according to the kind of intervention.

There should be a post-trial system of follow up to ensure longer-term adverse events are monitored and necessary healthcare to address any longer-term adverse effects are available to healthy volunteers.

While short term harms are immediately seen or felt, long-term harms are unprecedented. There should be a post-trial mechanism in place to ensure long-term monitoring and safety reporting (adverse drug reactions, adverse events, and serious adverse events, SUSARs, etc.) and healthcare for healthy volunteers. This system should ensure safety reporting are addressed as well as collect data on any additional adverse events that may develop post-trial.

This needs more emphasizes since healthy volunteers are more prone to long term harms

" And free/paid health care for healthy volunteers."

What about free post-trial follow-up?

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.

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.
Comments
Should is ambiguous, must is clearer. And/or clinics – so we would allow a sponsor not to have insurance? Think that is mis-aligned with GCP.
And relation with clinical trial should be determined by independent body.
Article 13. Insurance for research-related injury: There should be provisions to obtain comprehensive insurance coverage by sponsors and/or research clinics to cover all harms resulting from clinical trial participation, including post-trial care to address any lingering effects or complications stemming from trial-related injuries.
Can we add? The insurance policy should encompass a wide range of potential harms, including but not limited to physical injuries, psychological distress, and unforeseen medical complications arising from participation in the clinical trial. The insurance coverage should provide access to necessary medical treatments, therapies, and support services without facing undue financial burden. This includes coverage for medical expenses, rehabilitation costs, and any other related healthcare expenses incurred because of trial-related injuries. Sponsors should maintain transparent policies regarding insurance coverage, clearly outlining the scope of coverage, eligibility criteria, and claims procedures to ensure that participants are adequately informed and protected throughout the duration of the clinical trial.
Very good. This is the one article I think is an important improvement over the status quo, but it assumes that such coverage is available. If not, it may prohibit small universities and hospitals from running healthy volunteer trials. This could be particularly damaging to understanding the healthcare needs of rural patients. Still, it addresses an information problem (since the study organizers necessarily know more about the risks than the participants), provides something that participants may not be able to get on their own, and has a bounded cost.
One specific recommendation that would benefit healthy volunteers across the board is the explicit assumption of liability for long-term health problems and loss of income caused by trials. Companies that provide trials should provide high quality health AND disability insurance for all participants. There should be easy and clear steps for volunteers to raise health concerns that may be related to a trial they participated in. Personally I didn't experience long term impacts of my challenge, and I recognize that long term health impacts are rare, but it would be much more willing to sign up for trials. I felt that was the most salient and largest risk I was taking was getting encephalomyelitis or some other serious complication and losing my source of income or ability to do basic adls and iadls on a long-term basis. If that occurred, how would I fund my continued living and any care that I would need? This is reflected in 1DaySooner's suggestions for edits to article 13.

These adverse effects or injuries are not certain at the onset of the trial. How will you determine injuries related with the clinical trials as this can vary individually? Insurance needs to know specifically what they are covering. This can be tricky if not properly explored. The sponsor must provide insurance covering all adverse effects recorded by the pharmacovigilance unit during the clinical trial.

Please consider adding pre-screening: "...all harms caused by clinical trial participation, including pre-screening and post-trial care for injuries related with the clinical trial."

Add: "... including post-trial care for injuries related with the clinical trial and lost income or other incurred necessary expenses resulting from injury."

We support this provision and believe it can be made slightly more forceful with the proposed text

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

These must be double-checked to ensure that:

- a reputable insurer has been engaged;
- the period of the insurance is congruent with the clinical trial period;
- the number of participants covered by the insurance matches the proposal

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.

Comments

This one is very wooly for me, I would suggest removing. It is also partly covered in 3.

For introduction, consider :

Healthy volunteers often engage in clinical trials without the prospect of direct health benefits. Their decision to participate is frequently driven by the expectation of financial compensation, which becomes a pivotal motivation, especially when facing financial vulnerability. This reliance on compensation renders them particularly susceptible to exploitation, especially in situations of social disadvantage.

Additional info

Exploitation can manifest in various forms, including instances where research clinics unjustly leverage the financial needs of healthy volunteers. Such exploitation may involve offering inadequate compensation relative to the risks involved, imposing unreasonable demands, or failing to provide adequate safeguards for participant welfare.

Exploitation can exacerbate existing social inequalities, disproportionately affecting marginalized communities who may be more susceptible to financial pressures. In these circumstances, the ethical imperative to protect the rights, safety, and well-being of participants becomes even more crucial.

It is imperative for regulatory bodies, sponsors, and research institutions to establish comprehensive guidelines and oversight mechanisms to prevent and address exploitation of healthy volunteers within clinical trials. These measures should include transparent compensation policies, adequate safeguards for vulnerable populations, and avenues for reporting and addressing instances of exploitation.

By prioritizing welfare and addressing the socio-economic factors that contribute to vulnerability, stakeholders can uphold the principles of ethical research conduct and ensure that healthy volunteers are treated with dignity, fairness, and respect throughout their participation in clinical trials.

My inputs --- Article 14: Addressing situations of exploitation

In the realm of clinical trials, it is incumbent upon all stakeholders to vigilantly address potential situations of exploitation, particularly concerning healthy volunteers. Stakeholders must be equipped with the knowledge and tools necessary to identify circumstances where volunteers, both individually and collectively, may be vulnerable to exploitation.

This includes instances where financial compensation serves as a primary motivator for participation, placing volunteers at risk of exploitation due to their socio-economic circumstances. Stakeholders must remain vigilant and proactive in recognizing such vulnerabilities and taking appropriate steps to mitigate risks.

Education and awareness initiatives should be implemented to empower stakeholders with the requisite understanding and skills to identify and address potential instances of exploitation effectively. By fostering a culture of vigilance and accountability, stakeholders can uphold the principles of ethical conduct and ensure the protection and dignity of all participants involved in clinical trials.

Would it be a strong addition to mention a few examples of those risks of exploitation?

Who should do the education?

I believe it is not enough to address the risks as in just acknowledging a risk exists. I would rather use “mitigate” or “prevent” instead.

Who should do the education?

I believe it is not enough to address the risks as in just acknowledging a risk exists. I would rather use “mitigate” or “prevent” instead.

Use of term ‘exploitation’ is provocative and implies an inherent predatory aspect of clinical research enterprise. We suggest ‘undue influence’ as a more neutral term that does not assign de facto agency to any party, but rather is the result of confluence of certain factors in the clinical research domain, including participant vulnerabilities, payment, scientific zeal, recruitment practices, etc. While the charter is directed at specific stakeholders, the larger

stakeholder is the general public, and as was evidenced during the pandemic, public perception plays a key role in the success or failure of public health policy. Using terms like 'exploitation' have ramifications that may adversely affect public perception towards the clinical trial enterprise as a whole.

Suggest replacing The term 'exploitation' with 'undue influence.'

It is up to States to identify the varieties of potential exploitation situations by establishing a relevant legal and regulatory framework for healthy volunteers. Ethics Committees should be educated on how to identify collective circumstances that expose them to operational risks and ensure that measures to address them are applied at the level of individuals wishing to participate in or participating in trials

While it is desirable for all stakeholders to be sensitive to potential situations of exploitation and the circumstances in which volunteers are exposed to them, the Charter should go further by designating the bodies responsible for adjudicating such risks. In our view, this responsibility should be entrusted to the Ethics Committees referred to in Article 8. This would involve:

1. on the one hand, to commission with a view to better enforcing the law/regulations in force;
2. on the other hand, to leave as little room for personal judgement as possible, which can result in laxity or undue restrictions, the latter having a proven negative impact on the representativeness of the research.

As suggested in the commentary to Article 5, the expertise of ethics committees could be applied at the individual/trial level in conjunction with explicit legislation on collective circumstances leading to a risk of exploitation.

(Add following text)

International network of regulators should monitor development of global companies, in order to avoid disproportionated geographic allocation of early phases and late phases studies as well as post-trial access.

In addition, the requirement of trial registration in public database should be expanded to early phase clinical trials, in order to enable analysis of geographic allocation of trial sites.

As commented to Article 10, there is a need to prevent the exploitation of early phase clinical trials being conducted in low resource setting, especially in LMICs, due to the tightening of European regulations triggered by the case of TGN 1412. To this end, an international network of regulators is needed to monitor global companies to avoid disproportionated geographic allocation of early phases and late phases studies as well as post-trial access in terms of product development strategies. For this reason, the requirement of trial registration in public database should be expanded to early phase clinical trials, in order to enable analysis of geographic allocation of trial sites, because current international policy requires it only for late phase clinical trials.

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.

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.

Comments

Financial compensation. Compensation schemes should be transparent, commensurate with trial demands, and subject to ethical review to prevent undue inducement and safeguard trial integrity. 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.

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.

'across research fields' – not sure what we mean here.

Revised the first sentence to clarify that compensation is necessary but should be structured in ways that avoid the problems highlighted in this sentence. Revised the rest of the text for precision and clarity:

Financial compensation. Trial compensation should be structured in ways that discourage over-volunteering as well as concealment of health conditions and adverse events. Financial compensation should be reflective of the demands associated with each trial and approved by local ethics review boards. Guidance on fair and equitable compensation across research fields should be developed by policy makers. Trial information and informed consent documents should detail how payments will be made, including how early withdrawal from the trial will impact payment.

Reformulate for clarity “potential to compromise trial results by inducing concealment of health conditions and adverse events, “

I strongly support 1DaySooner’s suggestions for edits to section 15. While money wasn't my primary or even a major motivation to participate, losing 2 weeks of my free time, reduced ability to work, and vacation days used were a major cost to me. If I hadn't been paid adequately to compensate for those huge inconveniences I couldn't have justified the opportunity cost of participating, even though I really wanted to. I didn't participate for the money, but I wouldn't have been able to participate if there wasn't enough money provided to compensate for the costs to my life and the risks I was taking. In fact, I was barely able to afford it even with the compensation and almost had to drop out. More than one participant had to take off work, and some traveled long distances by plane or all-day car trips.

I don't foresee compensation resulting in concealment of health conditions except there are 'clauses' to this effect rather it can lead to over-volunteering. It can lead to over-volunteering.

Clinical and paraclinical inclusion assessment specific to clinical trials should be performed by third-party clinicians, independent of the trial. The results of this assessment should be entered into a database, allowing the healthy volunteer to be compared and potential risks assessed when the healthy volunteer is presented for another trial. Ideally, these data should be entered into the international database suggested in paragraph 1.

We strongly believe compensation is just and necessary in almost every study involving healthy volunteers. We understand that in some countries, there are laws and regulations that constrain or prohibit compensation to volunteers, and while we believe such regulations to be deeply misguided and harmful, we recognize that this charter cannot attempt to overturn them. Even so, we think it is morally imperative that payment not be stigmatised, and that this charter does not encourage medical research studies to offer less payment simply to be on the “safe side.”

Lowering compensation amounts does not protect participants. Rather, it means recruitment tends to draw from lower income groups, because the opportunity cost of participation is lower for them. Concerns over undue influence due to money are in reality just concerns about inadequate informed consent and the risk profile of a given study — but these are independent of compensation per se.

Suggest a payment frequency, e.g. a payment per visit, or every 2 or 3 visits?

Balance incentives to discourage serial participants and fair and equitable compensation for service in the country. Participant compensation should be disbursed fairly across the trial. Completion bonuses should be modest to encourage final outpatient study visits.

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.

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.

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.

Comments

Last part has previously been included in other articles, e.g. how to raise concerns and that staff must look after the wellbeing of the HVs. I would avoid duplication.

Lot of overlap here with 10&11. This section is about 'exploitation' remove and build into 10&11?

This could also be integrated into section 2. (It might be read as repetitive here, but there are also good reasons to have 'well-being' as a separate point).

Well-being during the clinical trial. Specific attention should be paid to ensure well-being of healthy volunteers during the trial. Clinical trial sites should identify and train staff members in charge of ensuring that healthy volunteers are treated respectfully, and that their well-being is ensured throughout the research process. Their daily needs, and special needs (if any) are addressed adequately without largely affecting their daily routine. 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, asking for help and from whom to seek these help, etc.

Select high quality phase I research clinics and design protocols to promote participants' well being and limit the welfare risks and harms.

This process needs to be managed in a manner that ensures no one is being coerced, that nothing untoward is happening, and that patients fully understand what they are getting themselves into. Writing from the point of view of South Africa, which has one of the highest youth unemployment rates in the World and is also the most unequal society in the world opportunities for exploitation are rife. RECs should take responsibility for assessing local needs. Participants need to be fairly compensated but this should not be in any way so attractive to harm them or induce them to co-enrolment.

To ensure that this takes place, some sort of monitoring is required – it is recommended that there is reporting as part of the protocol every 2 to 3 weeks signed by the study doctor, and that a complete checklist is included. These reports need to be shared with the sponsor and six months to the REC, similar to phase 2 and 3 trials.

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.
Comments
Key stakeholders, such as research ethics committees, research organisations, and regulators. It would be useful to reiterate these organisations' responsibilities. They are already mentioned in the preamble but it would be good to reinforce which organisations should be responsible here in conclusion.
This is far too vague (nice words without impact) when we have worked on explaining how to apply the 4 Rs
In introduction to 17, say "Being shown respect is an individual fundamental right" rather than "Respecting concerns is an individual fundamental right"
This should be article #1 (all stakeholders) and should be followed by subsections, each considering the main actions to be carried out by the different stakeholders
No definitions are offered of the 4Rs principles. I have made relevant suggestions for text to help the reader understand these principles: All stakeholders should carefully consider the application of the 4Rs principles — Respect for healthy volunteers and their contributions to science; Reduce the numbers of healthy volunteers in clinical trials to those needed to show safety and tolerability of tested interventions; Refine study interventions to support healthy volunteer welfare; Replace the use of healthy volunteers with the use of clinical patients where possible.
Recruitment strategies should be broad-based to include diverse genders and participants. However, current participation patterns often disproportionately enrol fairly young, male, economically disadvantaged or unemployed individuals and people of colour. Current practices indicate selection bias with serial participants and reduced external validity. Addressing this imbalance is crucial. Consequently, we have overrepresentation of individuals who are not representative and in the case of serial participants who are less susceptible to adverse events, drug safety data are seriously impacted and lack external validity.
This statement should be deleted. The concept of applying the 3Rs principle in animal studies to healthy volunteer studies by adding "respect" is inappropriate in the sense of deeming healthy volunteer trials to be analogous to animal studies. In particular, it is unclear whether the concept of "reducing" applies to human studies. Even in animal studies, there is a trade-off between reducing numbers and reducing suffering.
Recommend an explanation of what the 4Rs principles are and how these four terms apply in the context of clinical research.