GFREI :: Global Forum for Research Ethics & Integrity

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PUBLIC CONSULTATION SUBMISSION
VolREthics initiative :: DRAFT - Global Ethics Charter for the Protection of Healthy Volunteers in Clinical Trials

02 April 2024

Dear Colleagues:
By way of further introduction, I am writing from the context of the Global Forum for Research Ethics and Integrity [https://gfrei-ge2p2global.org/] – an open, global, collaborative forum of individuals from 30+ countries committed to advancing research ethics and integrity across the sciences. The Foundation referenced in my address block functions as GFREI's secretariat.

GFREI has engaged over 25 public consultation exercises over the last few years focused primarily around guidance, regulations and other norms-setting initiatives for biomedical research involving human participants. This work has involved, for example, the current revision of the *Declaration of Helsinki* and *ICH E6[R3],* the continuing development of WHO's *Best Practices in Clinical Trials,* and its current draft *Key criteria for the ethical acceptability of controlled human infection studies during public health emergencies.*

We observe that the global community is moving through an interesting and important period for the "global norms/guidance ecology" associated with biomedical research and human participant rights and protections. This period includes but is not limited to recent and upcoming revisions and new guidance noted just above, and certainly includes the *DRAFT - Global Ethics Charter for the Protection of Healthy Volunteers in Clinical Trials.*

GFREI is submitting separate comments on the draft *Global Ethics Charter* via the form provided for this exercise. However, we decided to also submit this letter as a complement to that form, assessing that the *General comments on the draft Charter* element of the form did not seem to provide an adequate vehicle to convey our overall thinking, and that the form did not provide space for comment on the draft's preamble or the introductory paragraphs for the article groups.

GFREI Observations/Recommendations

To begin and to be clear, we applaud INSERM's stewardship of the VolREthics Initiative and its processes**.** We align with Initiative's intent. We recognize the extensive regional engagement processes undertaken, the current public consultation, and the public meeting planned for April 2024 to move the draft forward. This approach has been and continues to be exemplary.

We employ below an assessment process that has emerged from our public consultation work as referenced. This approach integrates a focused number of parameters against which a draft guidance might be analyzed. It is intended to provide an orderly, transparent, rigorous and adaptable rubric which will inform our work in public consultations going forward, and which can be adapted and used by others. We consider it to be a public good.

Our assessment approach employ six parameters as depicted below and utilizes a set of due diligence questions associated with each to helps guide analysis and identify further questions and observations. We acknowledge the directness of our assessment language and trust it will be received as constructive to realizing the intent of the *Charter.*

1.0 Distinction; Specificity; Scope

:: Are issues/challenges addressed in the draft sufficiently distinct and specific?
:: Is the analysis sufficiently grounded in evidence to ground/scope the issue[s]?

We recognize and compliment the overall structure of the draft – leading with a preamble and providing thematic sections led by short context paragraphs supported by presumably relevant articles [see further discussion in 5.0 below].

Obviously, the preamble and the short context paragraphs are extremely important in articulating the issues at hand and in organizing the 17 articles in the draft, underscoring what make them distinct [necessitating new guidance] and helping clarify the intended scope of the charter.

But we observe, for example, that the preamble text seems to shift – paragraph to paragraph – on the scope of the charter and why – specifically – its issues are distinct from those treated in other guidance already in place [albeit not referenced].

For example, in the preamble, the rationale for the guidance ranges from recognition that no single charter can address the range of issues which may involve healthy volunteers, to establishing a highly specific focus for the draft, to addressing all stakeholders in all research fields which involve healthy volunteers:

> … The motivations to participate, the risks and benefits to which participants are exposed, and the ethical issues related to so many types of research are too diverse to be addressed in a single Ethics Charter. …
>
> … This Ethics Charter focuses on healthy volunteers involved in interventional clinical trials with medicinal products…

> … this Charter is addressed to all stakeholders potentially involved in medical research and beyond, including all research fields involving healthy volunteers.

Equally, there are definitional issues in the draft around what constitutes a "healthy" volunteer and what exclusion criteria might be operative across different types of trials integrating healthy volunteers.

For example, the draft is silent on the participation of adolescents/children in such research and what special considerations and protections might be appropriate. We assess that there are responsible research designs which might well require and strongly benefit from the participation of healthy young persons.

We are confident that the drafting group appreciates that "healthy volunteers" are not a unified group, especially as compared with patient groups defined in terms of a specific label indication. Such volunteers may participate in many types of clinical trials, and safety risks and uncertainties will differ among first-in-human trials of new pharmaceutical products as compared with an age-matched control group in a Phase 3 clinical trial as compared to a vaccine trial. Language clarifying such circumstances and characterizing the scope of both healthy volunteers and of the various types of clinical trials would therefore likely be a helpful addition.

Also on healthy volunteers, we are concerned that the draft is silent on those who might proceeding with "genuine" altruistic motivation – making an informed choice to participate in a study with high potential risk and largely unquantifiable potential harms. Instead, there is a characterization [without any cited evidence] that "…the prospect of financial compensation is most often the key motivation of healthy volunteers to take part in this type of medical research…:

In parallel, the draft is not specific about types of trials which may require separate, complementary guidance. Are CHIS studies included or excluded? Would studies that might include both patients and healthy volunteers require separate guidance?

We stress that these examples and those provided in other assessment areas below are indicative and not exhaustive.

Summary/Recommendation[s]
With regard to the due diligence questions *[italics above],* we do not assess that the issues/challenges addressed in the draft are sufficiently distinct and specific, that the scope is sufficiently clear, or that the analysis is sufficiently grounded in evidence.

We commend the Coordination Group's important work on the Charter to date, and recommend that its next draft address and strengthen its distinction, specificity, scope, and consider how references to evidence might support these attributes.

2.0 Necessity; Parsimony

:: Are the issues and how they are addressed/not addressed in the larger guidance/legal/regulatory ecology adequately explored/articulated?
:: Is there a material gap in that ecology such that new guidance is indicated?
:: Could the intent be secured through strengthening existing guidance[s]?

We note that the *Global Charter* draft does not position itself in the larger norms/guidance ecology which supports responsible conduct of clinical trials at the international level. Indeed, it does not

mention any other guidance documents, and does not analyze where other guidance may helpfully address common issues or where, specifically, they may fall short of doing so.

We raise this because we recognize that a number of global clinical development organizations publicly commit to conduct their research in alignment with, for example, the DoH, ICH GCP or CIOMS guidance, so "silence" on them in the *Global Charter* draft is not helpful.

In this context we note that in one of the "scientific publications" referenced in the bibliography of supporting content for the VolREthics Initiative, its working group members do reference such guidance as below:

> "…Similarly, ethical guidance for biomedical research — such as the Declaration of Helsinki from the World Medical Association*12*, the International Ethical Guidelines for Health-Related Research Involving Humans issued by the Council for International Organizations of Medical Sciences*13* and UNESCO's Universal Declaration on Bioethics and Human Rights*14* — do not address healthy volunteers as a specific subset of study participants..."
>
> *Nature Medicine (August 2023). "*The VolREthics initiative to protect the well-being of healthy volunteers in biomedical research*", by François Bompart, Jill A. Fisher, Elizabeth Allen, Esperança Sevene, Nandini Kumar, Chun Keat Chew, Valeria Fink, Dirk Lanzerath and François Hirsch. doi.org/10.1038/s41591-023–02490-6*

Equally, we note that while the draft's *Preamble* observes that "…very few countries have special legal provisions addressing the risks that healthy volunteers may face…", no examples of law or regulations which *do* have such provisions and no analysis about whether they have been effective is provided [see further comment in 6.0 below]. This absence lack of treatment is not helpful.

Summary/Recommendation[s]
With regard to the first due diligence question *[italics above]*, we do not assess that the draft – in any considered way – addresses how the issues of concern are addressed in the larger guidance/legal/ regulatory ecology.

With regard to the second due diligence question, we are concerned that while there may be gaps in the current guidance around these issues, scoping of that presumed gap is not rigorously or robustly addressed.

With regard to third due diligence question, and considering the above, we are cautious about simply accepting the draft's implied premise that current guidance cannot further evolve – especially during this volatile period of core guidance revisions – to adequately address the issues raised.

Overall, we argue that responsible stewardship of the norms/guidance ecology suggests reasonable [if not maximum} parsimony. Growing the number, format variety, or range of sources of normative guidances in this ecology should not be reasonably expected to improve its coherence, accelerate adoption of relevant guidance elements, or result in improved protections of human participants.

We commend the Coordination Group's important work on the Charter to date, and recommend that it strive in its next draft to address the concerns above.

3.0 Accountability; Stewardship

:: Does the draft identify accountability/ownership/jurisdiction[s] for its roles/recommendations/ imperatives? Are all relevant stakeholders addressed?

:: Is stewardship addressed [who owns the continuing evolution of the guidance]?

We certainly appreciate the range of stakeholders identified in the draft's *Preamble* and *Glossary* as below. Indeed, we observe that these two lists might be enriched further [e.g. industry organizations and professional/academic societies, both of which may issue relevant guidance for/on behalf of their members].

> *Preamble*
> "…The recommendations provided in this Charter are primarily intended for policy makers entrusted with protecting people's health in the regulation of clinical trials. However, given the crucial role played by other stakeholders, such as ethics committees, research organisations, regulators, health professionals, and healthy volunteers, in defining and implementing ethical and reliable standards, this Charter is addressed to all stakeholders potentially involved in medical research and beyond, including all research fields involving healthy volunteers…"
>
> *Glossary*
> *Stakeholders*: Key clinical trials stakeholders include healthy volunteers, investigators and their staff, lawmakers, regulators, study sponsors, Contract Research Organisations, policy makers, communities, media, and ethics review bodies.

While we agree that the broad stakeholder community as referenced must collaborate and act responsibly in their respective capacities to achieve the intended protections for healthy volunteers, we observe that the draft is either silent or marginal in its treatment of the role, responsibilities and imperatives associated with many, indeed most of these stakeholders.

Summary/Recommendation[s]
With regard to the first due diligence question *[italics above],* we do not assess that the draft successfully identifies all relevant stakeholders and does not successfully articulate for the stakeholders it does identify their respective accountabilities/ownership of the draft's recommendations/actions.

With regard to the second due diligence question, we do not see any clear language around who "owns" the charter's continuing stewardship in the longer term. It may, we suppose, be a continuing, funded INSERM program, but it could equally be a broader, public-private partnership that would best realize the Charter's aspirations. The draft is silent on this.

We commend the Coordination Group's important work on the Charter to date, and recommend that it strive in the draft's next version to address the specific roles/responsibilities/imperatives for all stakeholders, and the *Charter's l*ong term stewardship.

4.0 Completeness; Comprehensiveness

:: Is the draft's treatment of its focus/issues/recommendations both complete and comprehensive, such that the "material gap" has been adequately addressed?

We distinguish between guidance that evidences "completeness" in the sense that all relevant issues are identified and addressed at some level, from guidance that is comprehensive, evidenced by the depth of the analysis and guidance language for relevant issues. In short, we believe that guidance is ideally a healthy blend of completeness and comprehensiveness.

We observe that there are a number of issues in the draft that are not fully engaged and therefore not treated comprehensively.

One example is the draft's inventory and discussion of research staff roles and responsibilities in support of healthy volunteers [Articles 7, 9, 11, 16] and its silence on responsible protections and safeguards *for* research staff members.

A second example is *Article 2* and its call-to-action for countries to support heathy volunteer groups and roles that such groups might play.

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

This thinking is obviously modelled on patient advocacy groups, whose members enjoy common experience involving a particular condition or disease, and where the benefits of convening and collaborating are reasonably clear. This is much less clear for "healthy volunteers."

A comprehensive treatment of Article 2 would likely have acknowledged that patient groups for any disease are highly variable in terms of country presence globally, resourcing, maturity, and impact. A comprehensive treatment would likely have recognized that "countries" may have some supporting role but that such healthy volunteer groups would most often be civil society organizations competing for limited governmental resources with ?hundreds of other CSOs, each focused on a unique issue or interest.

A third example is *Article 4* and its suggestion that the proposed "mandatory system" might be managed by regulators or the private sector.

> *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

While including the issue of "over-volunteering" certainly supports the "completeness" of the draft in terms of the issues it identifies, the treatment of the issue [depth] is extremely limited [indeed naïve about governance, costs, confidentiality and data protections, and more], weakening its "comprehensiveness."

A fourth example is the glossary, where its presence contributes to the completeness of the draft, but the actual definitions for terms provided, and limited number of terms addressed, are indicative of weak comprehensiveness.

Summary/Recommendation[s]
With regard to the due diligence question *[italics above],* we do not assess that the draft's treatment of its focus/issues/recommendations is both complete and comprehensive, or that the "material gap" in

current guidance has been adequately addressed.

We commend the Coordination Group's important work on the Charter to date, and recommend that it strive in its next draft to address these systemic weaknesses.

5.0 Coherence; Concision

:: Is the draft and its elements/structure/treatment coherent and concise such that it presents its observations/recommendations/imperatives/calls to action in an effective fashion?

We appreciate the apparent intent to strengthen the coherence of the draft via its structure – leading with a preamble and providing thematic sections led by short context paragraphs supported by presumably relevant articles.

Beyond structure, coherence depends on each element of the draft contributing to and enhancing the overall guidance work product and that its arguments are presented in an effective fashion. While assessments of "an effective fashion" are, to some degree, subjective, there are important signals to be aware of.

For example, our multiple readings of the draft's text were too often paused by representations that were questionable [in factual terms and not otherwise supported by evidence/ literature, etc.], or distinct in any important way from what "patient volunteers" might well experience, expect or deserve.

Article 10 and 12, as below, provide just two examples. We do not appreciate that heathy volunteers and patient volunteers need or deserve anything different in terms of what the article argues is necessary and responsible.

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

Further, we found the closing section paragraph – introducing the 4Rs principle [Respect, Reduce, Refine, Replace] as "a foundational guide for safe, ethical, and reliable clinical research" with its own *Article 17* calling for careful consideration of the 4Rs – to be particularly challenging.

This principle is not signaled earlier in the draft and, as an apparently overarching principle, is not integrated or mapped to the earlier 16 articles in any helpful way. No evidence or literature about this principle is provided and it is unclear to us what compelling value it adds to the charter. Its presence does *not* contribute to the charter's coherence.

We do recognize and applaud that the draft is concise overall at 4 pages excluding glossary.

Summary/Recommendation[s]

With regard to the due diligence question *[italics above],* we do not assess that the draft in its current version presents its observations/recommendations/imperatives/calls to action in an effective fashion due to coherence issues at various points. We do recognize its concision as a strong positive.

We commend the Coordination Group's important work on the Charter to date, and recommend that it strive in the draft's next version to address the coherence issues as indicated in the discussion above.

6.0 Operationalization; Assessment

:: Does the draft articulate how its recommendations/imperatives/etc. can be operationalized? Are they actionable and realizable in practical terms?

:: Are assessment strategies addressed enabling measurement of impacts and refinement?

We observe that throughout the draft those stakeholders which *are* referenced [see 3.0 above] are charged to do x or y or z. Examples include:

:: Countries should… – Articles 1,2,3, 15
:: Sponsors – Article 13
:: Research clinics – Articles 11, 13
:: Clinical trial sites – Article 16
:: Regulators – Article 4
:: Private sector – Article 4
:: Ethics review boards – Articles 7, 8, 15
:: All stakeholders – Articles 14, 17

But we also observe that these calls-to-action/imperatives do not offer any suggestions or guidance around *how* the recommended actions might be implemented, what resources might be required, what challenges might be expected.

Equally, a number of articles in the draft argue for a condition or practice that would benefit healthy volunteers, but do not identify the specific stakeholder or stakeholders who might properly implement or achieve the outcome. *Article 12. Monitoring of potential long-term harms* would be an example.

No templates, best practice examples, case studies, or references to the literature are provided for any of the actions discussed in the draft, so we assess the draft is presuming that stakeholders have the organizational capacity, resources, strategies and political will to simply proceed as recommended. We are much less sanguine on this.

Summary/Recommendation[s]

With regard to the first due diligence question *[italics above],* we do not assess that the draft successfully articulates how its recommendations and imperatives can be operationalized, and question how actionable and realizable some of them may be in practical terms.

With regard to the second due diligence question, we do not see any clear language addressing assessment strategies enabling measurement of impacts of the recommendations, or how such strategies might support the Charter's continuing refinement.

We commend the Coordination Group's important work on the Charter to date, and recommend that it strive in its next draft to address the deficits discussed above.

Overall Assessment/Recommendation

Again, we applaud the intent and the processes undertaken in developing this draft charter to address the many important issues around healthy volunteers in clinical research.

Mindful that the current public consultation process undertaken by the VolREthics Initiative/INSERM has generated a number of interventions [30+], we recommend that the Coordination Group take the necessary time to reflect, reconsider, re-engineer the draft and the timing of its roll-out .

Achieving the Charter's aspirations in ensuring necessary protections for, and ensuring the rights of, healthy volunteers should be the guiding imperative.

We would be happy to discuss this intervention directly with you as may be helpful.

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