Incorporating Post-Clinical Trial Access Requirements in the WHO INB Negotiation Text

Technical Note

The issues

The current version of the INB proposal draft for negotiation text includes several important provisions for improving R&D capacity, clinical trial collaboration and sharing of research data and results under Article 9. Article 12 also includes biomedical research under the pathogen access and benefit sharing (PABS) system. However, overall there is an absence of reference to international medical ethics and legal standards concerning post-clinical trial access to the end products, and to protect patients' rights in the research context.

In our view, this shortcoming compromises an important leverage that can substantively support equity. To strengthen the provisions concerned, the text should include a direct reference to, and incorporate, existing international medical research ethics standards. In the draft text dated February 19, 2024, **Article 9.3 (d) ii introduced an important provision on guaranteeing access to the end products for the population or community in which research is carried out**. However, this provision was deleted in the recently published INB draft text on March 08, 2024. The note elaborates the rationale, feasibility and necessity of reinstating Article 9.3 (d) ii in the INB negotiation.

Rationale and feasibility

Clinical trials are indispensable practices for all biomedical research and product development processes. Clinical trials involving humans are governed by globally known medical ethics standards and are subject to regulatory approval by public health authorities in all countries.

The Declaration of Helsinki of the World Medical Association explicitly includes the notion of supporting post-trial access to the end products, particularly for participants who still need an intervention identified as beneficial in the trial. This provides an important protection for individuals/participants who support and join clinical trials.

The International Ethical Guidelines for Health-related Research Involving Humans, known as the CIOMS guidelines -- published by WHO and the Council for International Organizations of Medical Science -- expands the concept of post-trial access to include other benefits targeting not only participants of clinical trials, but also the communities where trials are hosted, particularly when the research is carried out in resource-limited settings. It is important to clarify that the CIOMS guidelines consider that low-resource settings can be situated in both LMIC and HIC.

Another ethical recommendation from CIOMS pertains to the establishment of post-trial access plans to make sure that medical products are made available (registered) and affordable for the local communities and health authorities where they were trialed (Guideline 2). These plans should consider the conditions of authorisation for distribution, and decisions regarding payments, royalties, subsidies, technology and intellectual property, as well as distribution costs.

Additional benefits, such as capacity building to improve the health infrastructure, training laboratory personnel, and educating the public about the nature of research and the benefits resulting from a particular study, are also included in CIOMS guidelines.

Post-clinical trial access requirements are applicable to all types of biomedical products developed through clinical trials. The responsibilities to ensure access in this context are shared among multiple stakeholders involved in clinical trials, including: sponsors, implementers, ethical review committees, research councils, and regulatory agencies who are responsible for registering clinical trials.

Post-clinical trial access as a condition arising from conducting clinical trials is different from other conditionalities in the context of biomedical research that are proposed in the INB negotiation:

	Legal basis	**Scope of products covered**	**Triggers for the conditions**	**Who can request the conditions**	**Direct beneficiaries**	**Relevant INB draft provisions**
Post-clinical trial access	National clinical trial regulations	All products that require clinical trials	Conducting a clinical trial	Ethical review board/committee; regulatory authority	Clinical trial participants and communities in clinical trial-hosting countries	Article 9, 12
Access conditions in public funding for R&D	Research agreements/contracts	All products that are developed with public funding	Receiving public funding for R&D	Government agency that approves public funding	Depending on the conditions, benefiting global access needs and developing countries in particular	Article 9, 10, 11
Benefit-sharing conditions in WHO PABS mechanism	Rules on PABS and Standard Material Transfer Agreement clauses	Products developed by using materials from WHO PABS mechanism	Accessing materials from WHO PABS mechanism	WHO PABS mechanism	WHO and WHO-coordinated initiatives that benefit global access needs and developing countries in particular	Article 12

Although post-clinical trial access provides an additional leverage point to protect access to the end products, it is not followed in many instances, especially in developing countries, either through non-registration of end products in countries that join trials, or by charging unaffordable prices, or due to lack of reliable supply, among other actions. This non-compliance can be attributed to the fact that most medical ethics standards are non-binding instruments, and robust global norms to uphold these standards as well as international collaboration between public health authorities to ensure compliance when approving clinical trials, is lacking.

Based on the above rationale, it is feasible and beneficial to incorporate post-clinical trial access requirements in Article 9 in the context of INB negotiation. This would:

- Provide an important safeguard for fair distribution of the benefits and burdens of hosting and contributing to clinical trials. Benefit sharing and post-trial access requirements apply to all types of clinical trials, on all types of medical interventions and products involving human, regardless of whether the research involves the use of the WHO PABS mechanism or the use of public funding;
- Speak to the global biomedical research community, including industry researchers, who are already familiar with medical ethics requirements in the context of seeking ethical review of the clinical trial protocol and registration of the clinical trials with regulatory authorities; and

- Empower public health authorities in all countries in the context of regulating clinical trials and protecting patients' rights, and provide a benchmark for enhancing international collaboration of R&D, as envisaged by the current INB draft.

Reinstating Article 9.3(d) ii will clarify governments' responsibilities

Based on the above analysis, **we call for reintroduction of Article 9.3 (d) ii** into the INB negotiation text in order to clarify governments' obligation to guarantee access to end products for the population and communities in which the research is carried out through the below options:

- Developing, strengthening or improving national regulatory frameworks and/or practices concerning approving, registering and overseeing clinical trials initiated by entities in its territory, and/or conducted in its territory, or as part of international multi-centre clinical trial collaborations;
- Developing, strengthening or improving compliance mechanisms, in liaison with relevant medical ethics review authorities in countries, to facilitate the compliance of post-clinical trial access requirements by all relevant entities conducting clinical trials;
- Collaborating with other governments to exchange best practices in order to improve international standards and protections in this regard; and
- Collaborating with other governments to ensure international, multi-centre clinical trial protocols fully incorporate and comply with post-clinical trial access requirements.

Sources in existing international instruments and standards

WHA 75.8 Resolution: Strengthening clinical trials to provide high-quality evidence on health interventions and to improve research quality and coordination in research

> **"**Underscoring that clinical trials should be health-needs driven, evidence based, well designed and well implemented and be guided by established ethical guidance, including principles of fairness, equity, justice, beneficence and autonomy; and that clinical trials should be considered a shared responsibility**"**

International Ethical Guidelines for Health-related Research Involving Humans, published by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the WHO

> **Guideline 2:** Research conducted in low-resource settings
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> "make every effort, in cooperation with government and other relevant stakeholders, to make available as soon as possible any intervention or product developed, and knowledge generated, for the population or community in which the research is carried out, and to assist in building local research capacity. In some cases, in order to ensure an overall fair distribution of the benefits and burdens of the research, additional benefits such as investments in the local health infrastructure should be provided to the population or community"
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> "Post-trial availability for communities and populations. Even if research addresses a question that has social value for the community or population where it is carried out, the community or population will not benefit from successful research unless the knowledge and interventions that it produces are made available to them and products are reasonably priced. Post-trial access plans are of particular concern for research conducted in low-resource settings where governments lack the means or infrastructure to make such products widely available."

"Responsibilities and plans. When the research has important potential individual benefits to the population or community, the responsibility to make any intervention or product developed available to this population is shared among researchers, sponsors, governments, and civil society. For this reason, the negotiation among stakeholders must include representatives in the community or country, including, where appropriate, the national government, the health ministry, local health authorities, relevant scientific and ethics groups, as well as members of the communities from which persons are drawn, patent-holders if they are other than the sponsor, and nongovernmental organizations such as health advocacy groups. The negotiation must address the health-care infrastructure required for safe and appropriate use of any intervention or product developed. When applicable, it must also consider the likelihood and conditions of authorization for distribution, and decisions regarding payments, royalties, subsidies, technology and intellectual property, as well as distribution costs, when such information is not proprietary. A plan to ensure the availability and distribution of successful products can require engaging with international organizations, donor governments and bilateral agencies, civil society organizations, and the private sector. The ability of the local healthcare infrastructure to be able to provide the intervention must be facilitated at the outset so that delivery is possible following the completion of the research."

"Additional benefits to the population or community. Benefits other than those associated with study participation may accrue to the community or population, especially in resource-poor settings. Such benefits can include improving the health infrastructure, training laboratory personnel, and educating the public about the nature of research and the benefits resulting from a particular study. Whereas capacity-building should be a part of any research conducted in low-resource settings, other types of benefits will depend on the circumstances of the research and environment in which it is carried out. These additional benefits must be determined in consultation with the communities or the local population. Additional benefits may also include contributions that research or research partnerships make to the overall scientific environment of such countries and communities."

Guideline 3: equitable distribution of benefits and burdens of in the selection of individuals and groups of participants in research

"Sponsors, researchers, governmental authorities, research ethics committees and other stakeholders must ensure that the benefits and burdens of research are equitably distributed. Groups, communities and individuals invited to participate in research must be selected for scientific reasons and not because they are easy to recruit because of their compromised social or economic position or their ease of manipulation. Because categorical exclusion from research can result in or exacerbate health disparities, the exclusion of groups in need of special protection must be justified. Groups that are unlikely to benefit from any knowledge gained from the research should not bear a disproportionate share of the risks and burdens of research participation. Groups that are under-represented in medical research should be provided appropriate access to participate."

World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects

Post-Trial Provisions

"34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process."

REFERENCES

[1] The Nagoya Protocol on Access and Benefit-sharing

[2] CIOMS International Ethical Guidelines for Health-related Research Involving Humans

[3] The World Medical Association Declaration of Taipei

[4] The World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects

[5] WHO Joint Statement on Public Disclosure of Results From Clinical Trials