
Strengthening clinical trials to provide high-quality evidence on health interventions and to improve research quality and coordination

Report by the Director-General

1. In May 2022, the Seventy-fifth World Health Assembly adopted resolution WHA75.8 on strengthening clinical trials¹ to provide high-quality evidence on health interventions and to improve research quality and coordination.
2. Recognizing that “well-designed² and well-implemented clinical trials are indispensable for assessing the safety and efficacy of health interventions” and acknowledging “the importance of promoting equity in clinical trial capability” the Health Assembly sought to improve the quality of evidence generated in clinical trials and their coordination. It noted that “clinical trials on new health interventions are likely to produce the clearest result when carried out in diverse settings, including all major population groups the intervention is intended to benefit, with a particular focus on under-represented populations”; these may refer to women, in particular pregnant and lactating women, children and other populations that are under-represented in clinical trials such as vulnerable and marginalized people. In addition to several requests to the Director-General, the Health Assembly identified several possible actions for clinical researchers, trial sponsors, research funders, research ethics committees and national regulatory authorities that are key elements of the clinical trials ecosystem.

STEPS TO IMPLEMENT RESOLUTION WHA75.8 INCLUDING CONSOLIDATED INPUTS FROM THE CONSULTATIONS REQUESTED BY THE HEALTH ASSEMBLY

3. In resolution WHA75.8 (2022) the Health Assembly requested the Director-General, inter alia, “to organize, in a transparent manner, stakeholder consultations, in line with the Framework of

¹ “A clinical trial is defined by WHO as any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Clinical trials may also be referred to as interventional trials. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc. This definition includes Phase I to Phase IV trials.” Joint statement on public disclosure of results from clinical trials, 2017 (<https://www.who.int/news/item/18-05-2017-joint-statement-on-registration>, accessed 25 May 2022).

² Throughout the resolution “well-designed trials” refers to trials that are scientifically and ethically appropriate. For submission to medical product regulatory authorities, trials should adhere to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines and some Member States may consider International Coalition of Medicines Regulatory Authorities guidelines. In order to generate evidence that is robust enough to support decision-making, such as widespread use of therapeutics or preventives, trials should be designed, conducted, analysed and reported appropriately. A well-designed trial must also be practically feasible to conduct.

Engagement with Non-State Actors, with Member States, nongovernmental organizations including patient groups, private-sector entities including international business associations, philanthropic foundations and academic institutions, as appropriate, on the respective roles of the WHO Secretariat, Member States¹ and non-State actors, and to identify and propose to Member States, for consideration by the governing bodies, best practices and other measures to strengthen the global clinical trial ecosystem, taking into account relevant initiatives where appropriate”.

4. To initiate the response to the mandate,² a document that framed questions was circulated in August 2022 to all technical departments in the Secretariat to gather input. Following this, the Secretariat arranged an internal coordination meeting on implementing resolution WHA75.8 (2022) in order to identify existing initiatives, priorities and synergies, and to collaborate on key items needed to operationalize the resolution. Technical departments were asked to encourage stakeholders to submit their inputs on major issues that they wanted to be included in the report on the stakeholder consultations requested by the Health Assembly.

5. In October 2022, a public consultation page was opened on the WHO website to receive inputs and comments from the Member States and non-State actors pursuant to the resolution, in order to collate inputs on the roles of Member States,¹ non-State actors and the Secretariat, as well as recommendations on best practices and other measures to strengthen the global clinical trial ecosystem, taking into account other initiatives where appropriate, for consideration by the governing bodies.

6. The Secretariat held a consultation for Member States on 6 October 2022 and for non-State actors on 7 October 2022. The two meetings focused on introducing the online consultation that took place from 12 October 2022 to 11 November 2022 and on what improvements are needed in the global clinical trials ecosystem in normal times as well as during public health emergencies of international concern. The inputs received are summarized in this report, and it is intended to make a longer report on the consultation available before the Board’s session. As much important information was contained in the extensive submissions, the Secretariat is seeking permission to make the full inputs publicly available and will do so once that permission is received.

7. The outcome of the online consultation supported the role of WHO in convening and thus generating research priorities at the global level. WHO’s R&D Blueprint has published several documents that support the generation of high-quality evidence related to epidemic and potentially pandemic pathogens and diseases.³ These publications range from research and development road maps, target product profiles, and consensus trial designs including endpoints, to the coordination of stakeholders. The Secretariat has developed standard procedures for defining research priorities and target product profiles in all disease areas. More than 20 such profiles have been published on the basis of harmonized procedures over the past two years.⁴

¹ And, where applicable, regional economic integration organizations.

² The Secretariat has developed a webpage gathering information and resources of relevance to resolution WHA75.8 (<https://www.who.int/our-work/science-division/research-for-health/implementation-of-the-resolution-on-clinical-trials>, accessed 15 December 2022).

³ WHO. R&D Blueprint (www.who.int/teams/blueprint, accessed 21 November 2022).

⁴ WHO. Target product profiles. Geneva: World Health Organization (<https://www.who.int/observatories/global-observatory-on-health-research-and-development/analyses-and-syntheses/target-product-profile/who-target-product-profiles>, accessed 10 November 2022).

8. A mapping exercise of clinical trial networks conducted after the adoption of resolution WHA75.8 revealed gaps in some regions.¹ Stakeholders that have conducted mapping exercises are encouraged to share the results with the Secretariat for inclusion in the more comprehensive mapping underway of the ecosystem that will form a baseline for its further work.

9. The Global Accelerator for Paediatric Formulations is a WHO-coordinated network that plays an important role in prioritizing paediatric research in different disease areas. It will contribute to operationalizing resolution WHA75.8 by streamlining the generation of clinical evidence and promoting best practices for paediatric medicines research and development.²

10. The WHO International Clinical Trial Registry Platform has recently developed harmonized guidance on the results-related elements that should be reported in clinical trial registries. It will support Member States to facilitate implementation of this guidance by trial registries and policy-makers.

11. During the consultations in October to November 2022, 273 inputs were received, of which 53 were from Member States, including government agencies, and 63 were from non-State actors. Key outcomes of the consultation are as follows.³

- The major strategic gap lies in the overarching system for strengthening the clinical trials ecosystem so that capabilities that exist in normal times can be applied in emergencies. The following were all identified as vital needs for such strengthening: work to augment the capacity for clinical trials (personnel and infrastructure) particularly in low- and middle-income countries; further development of clinical trial networks for coordination and data sharing; national and international processes for prioritization, with political support, to inform research questions that must be addressed in order to change policy through large-scale randomized clinical trials; development of institutional research competencies required to implement trial procedures appropriately; systems and personnel to manage, analyse and share data securely while respecting national regulations; procedures for prompt reporting of complete results disaggregated by sex, age and other important variables, including means to share underlying trial data sets once identifying information has been removed and patients anonymized; recognition of the central role of patients and communities in the ecosystem; and ensured sustainability of any improvements made to the ecosystem.
- The public consultation highlighted the crucial importance of (and existing gaps in) the strengthening of national regulatory authorities and national ethics committees, and the great need for harmonization of the many different review procedures between countries and committees. This lack of regulatory and ethics review harmonization is a barrier to efficiency and timeliness, given that many research priorities can only be addressed through multinational trials.

¹ WHO. Rapid scoping study on global clinical trials infrastructure – Final Report (December 2021). Geneva: World Health Organization; 2021 (<https://tdr.who.int/docs/librariesprovider10/essence/rapid-scoping-study-report.pdf>, accessed 10 November 2022).

² WHO. Global Accelerator for Paediatric Formulations Network (GAP-f). Geneva: World Health Organization (<https://www.who.int/initiatives/gap-f>, accessed 10 November 2022).

³ A supplementary report with more extensive summaries of the inputs received is available at <https://www.who.int/publications/m/item/supplementary-report-on-implementing-wha-resolution-75.8-on-strengthening-clinical-trials-to-provide-high-quality-evidence-on-health-interventions-and-to-improve-research-quality-and-coordination>, accessed 5 January 2023.

- Almost all respondents discussed the considerable need for greater capacity for trials in lower-income countries with a greater focus on country leadership in clinical trials, and equitable partnerships for research in such countries. This expanded capacity includes stronger engagement with authorities in these countries, and a better focus on factors beyond regulatory authorization, including affordability, availability and suitability to assist in ensuring more rapid and equitable access to new technologies.
- There was support for new trial modalities, such as decentralized and paperless clinical trials, that incorporate patient perspectives, mobile technologies and telemedicine.
- The coronavirus disease (COVID-19) pandemic has highlighted the benefits of cross-sectoral and innovative approaches to support adaptive, multicountry platform trials, linked where possible to pre-positioned master protocols, so as to rapidly generate data that support regulatory authorization and guidelines processes. The need was identified to develop harmonized procedures to better enable timely conduct of high-quality multicountry trials that address national and international research priorities. Weaknesses identified include excessive bureaucracy and the waste created by the conduct of many poorly-designed and uninformative trials.
- Greater international collaboration and coordination were highlighted as a significant need for efficient funding of agreed priorities and for multinational and multiregional trials where appropriate. At present, effective coordination mechanisms are lacking for trials and funding in all WHO regions and disease areas.
- A need was identified for ways to enable greater agility in procedures and their application for pivoting capacities for trials from normal times to emergencies, including expedited approval timelines in emergencies in all countries.
- Gaps in data on specific population groups and disease targets, and gender biases in data, which may result in these groups being precluded from access to needed interventions were highlighted. Such information includes, but is not restricted to, paediatric data and data from pregnant and breastfeeding women. Weaknesses included inadequate reporting of data disaggregated by sex and gender and relating to WHO's priority pathogens such as those for neglected tropical diseases and in the R&D Blueprint, and in the area of new antibiotics for highly-resistant pathogens. Actions are needed to fill these gaps in the global evidence base.

12. Contributors stated their expectation that the Secretariat will proceed with reviewing the existing guidance and will publish the results of its mapping of the baseline of the ecosystem, including infrastructure, capabilities, standards, governance processes (including national regulatory authorities and research ethics committees), networks, trials registration and relevant regulations. The Secretariat has initiated, following standard WHO processes, the development of new guidance for clinical trials quality and ecosystem strengthening, with an internal steering group having been constituted, as requested in resolution WHA75.8 (2022). A draft of the new guidance should be available for consultation with stakeholders by late 2023. The Secretariat is reviewing the available existing guidance including that from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, a report on clinical research in resource-limited settings,¹ guidance for

¹ CIOMS. Clinical research in resource-limited settings: A consensus by a CIOMS working group. Geneva: Council for International Organizations for Medical Sciences; 2021 (cioms.ch/publications/product/clinical-research-in-low-resource-settings/, accessed 10 November 2022).

good randomized clinical trials¹ and recent literature on clinical trials methods as a starting point. In order to support Member States in strengthening their regulatory system as urged in resolution WHA67.20 (2014) on regulatory system strengthening of medical products, the Secretariat uses a Global Benchmarking Tool for Evaluation of National Regulatory System of Medical Products.² In addition to help for building capacity for the ethics oversight of research, it published in October 2022 a draft version of a WHO tool for benchmarking ethics oversight of health-related research with human participants.³ The Secretariat is proceeding with the rapid development of guidance and will include a status update in its report to the Seventy-sixth World Health Assembly.

13. As the Secretariat develops the guidance requested in resolution WHA75.8 (2022), it intends also to develop a self-assessment tool with indicators for the maturity of the clinical trial ecosystem at national and international levels, aligned with the framework of the resolution.

ACTION BY THE EXECUTIVE BOARD

14. The Board is invited to note the report; it is further invited to consider the following questions.

- In line with resolution WHA75.8, how best can the Secretariat provide support to Member States and other stakeholders in mapping existing national infrastructure, capabilities and large trial networks capable of rapidly implementing large-scale, high-quality trials as the need arises and covering all relevant levels of the health system, including primary health care?
- What is the Board's view of the Secretariat's plan set out in paragraph 13 to elaborate a self-assessment tool for clinical trial ecosystems?

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¹ The Good Clinical Trials Collaborative: new proportionate guidance for Randomized Controlled Trials (RCTs) (www.goodtrials.org, accessed 10 November 2022).

² WHO. WHO Global Benchmarking Tool (GBT) for Evaluation of National Regulatory System of Medical Products Revision VI. Geneva: World Health Organization; 2021 (<https://www.who.int/publications/i/item/9789240020245>, accessed 10 November 2022).

³ WHO. WHO tool for benchmarking ethics oversight of health-related research with human participants. Geneva: World Health Organization; 2022 (<https://www.who.int/publications/m/item/who-tool-for-benchmarking-ethics-oversight-of-health-related-research-with-human-participants>, accessed 10 November 2022).