

**WHO Stakeholder consultation related to WHA 75.8:  
“Strengthening clinical trials to provide high-quality evidence on health interventions and to improve  
research quality and coordination”**

**Introduction and discussion questions**

**I. Introduction**

The WHO Secretariat is organizing stakeholder consultations as instructed by WHA 75.8 “Strengthening clinical trials<sup>1</sup> to provide high-quality evidence on health interventions and to improve research quality and coordination”

<sup>1</sup> “WHO defines a clinical trial 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.” WHO ICTRP.

The first action for the WHO secretariat is as follows:

(1) to organize, in a transparent manner, stakeholder consultations, in line with the Framework of 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 States 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.

While the resolution does not define “clinical trials ecosystem” the secretariat is using the following definition of the clinical trials ecosystem based on the wording of the resolution: the clinical trials ecosystem is the sum of all elements required to fund, prioritize, design, conduct, monitor and report scientifically and ethically appropriate, well-designed, and well-implemented clinical trials as well as features necessary for oversight and coordination.

Such trials should generate high quality scientific data and evidence that inform the scientific state of the art as well as both regulatory decision-making and clinical guidelines processes related to new or existing interventions including through comparative effectiveness, and cost-effectiveness studies. The resolution states 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.” The elements of the ecosystem may include but are not restricted to: regulations and legislation governing the suitability of data generated for regulatory assessment by national regulatory authorities as well as oversight by research ethics committees; infrastructures as well as institutional and individual research competencies required to implement trial procedures appropriately; systems and personnel to manage, analyse and share data securely respecting national regulations; procedures to report results promptly with a focus on transparency and, increasingly, procedures to share underlying trial datasets once patient de-identification and anonymization have occurred.

Other ecosystem elements include the availability and method of deployment of financial resources, whether from the private or public sectors, to conduct clinical trials and how these are allocated; clinical trials networks and prioritization processes to identify research questions, populations, interventions, comparator groups, and outcomes to be addressed in well-designed trials. Coordination between different elements forms part of the ecosystem. The unmet health needs and disease burden of individuals and populations are related to the ecosystem through the prioritization processes for the utilization of clinical trial structures. The resolution discusses the application of clinical trials in normal times and the need for specific provisions for rapid deployment of clinical trial capacities in times of a WHO-designated Public Health Emergency of International Concern.

## Questions for stakeholder consultation:

### Introductory question

The following questions go into some detail on elements of the ecosystem, requesting structured inputs.

Before this, we would like to request your overall key inputs on “recommendations for best practices and other measures to improve the global clinical trials ecosystem, taking into account existing initiatives”. This may include the role of WHO, Member States and non-State actors. It may also include elements on 1) prioritization of funding and trials, 2) improving quality of the overall evidence generated by the ecosystem including infrastructure, capabilities, standards, governance processes 3) improving collaboration and coordination, and 4) improving translation of results to policies and licensure/authorization.

Please share the key elements of your overall input to the submission below:

The **European Society for Medical Oncology (ESMO)** (<https://www.esmo.org>) is a global network of more than 25,000 cancer professionals from over 160 countries. Our members, who are mainly medical oncologists, treat cancer patients and perform clinical trials.

The **ESMO Clinical Practice Guidelines** (<https://www.esmo.org/guidelines>), used by oncologists around the world to treat and care for cancer patients, are based on scientific evidence from clinical trials. ESMO addresses issues related to clinical trials through the expertise of the **ESMO European Policy Committee** (<https://www.esmo.org/policy/european-policy-committee>), the **ESMO Clinical Research Observatory Task Force** (<https://www.esmo.org/research/esmo-clinical-research-observatory-task-force>), the **Clinical Academic Cancer Research Form (CAREFOR)** (<https://www.esmo.org/policy/carefor-the-clinical-academic-cancer-research-forum>), and the **ESMO Faculty** (<https://www.esmo.org/about-esmo/organisational-structure/esmo-faculty>). Moreover, ESMO is a major contributor to dissemination of scientific output generated from cancer clinical trials as well as to trialist networking via its scientific congresses and meetings.

Therefore, ESMO welcomes the opportunity to be able to participate in the WHO consultation related to resolution (WHA 75/8) on [Strengthening clinical trials to provide high-quality evidence on health interventions and to improve research quality and coordination](https://apps.who.int/gb/ebwha/pdf_files/WHA75/A75_R8-en.pdf) ([https://apps.who.int/gb/ebwha/pdf\\_files/WHA75/A75\\_R8-en.pdf](https://apps.who.int/gb/ebwha/pdf_files/WHA75/A75_R8-en.pdf)), which has the intent to foster evidence-based research to improve health and patient outcomes worldwide.

Regulating clinical trials is a complex task, and if WHO decides to produce international guidelines, these need to be harmonised with national regulations which may vary considerably across the globe. Any measures supporting clinical trials should address the following issues:

1. Enabling the regulatory environment: Ensure that any international guidance must respect the principles and high standards as defined by the [Declaration of Helsinki](https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) (<https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>), and the guidelines for [Good Clinical Practice \(GCP\)](https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice) (<https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice>) as well as national and local regulations that guarantee patients' safety and rights and the scientific integrity of data. They should be comprehensive, and implemented in a consistent and harmonized way with national and regional guidelines on clinical trials, as well as other topics affecting them such as data protection and cross-border use of health data and biological materials. For example, to facilitate clinical trials in the European Union, it is of utmost importance that the [EU Clinical Trials Regulation](https://www.esmo.org/policy/eu-clinical-trials-regulation) (<https://www.esmo.org/policy/eu-clinical-trials-regulation>) is implemented harmoniously across EU Member States. Access to patient data is regulated through the [EU General Data Protection Regulation \(GDPR\)](https://www.esmo.org/policy/eu-general-data-protection-regulation) (<https://www.esmo.org/policy/eu-general-data-protection-regulation>) which necessitates reducing existing differences in the interpretation of the Regulation at the country level so that it is

implemented in a consistent manner in all EU Member States. Topics of particular importance for harmonization in the GDPR are recitals 33 (principle of 'one-time withdrawable patient consent' for retrospective research) and 157 (principle of 'no consent' for population-based registries) of the GDPR which are necessary to facilitate clinical research. In addition, patients must have access to the most useful precision medicine tests and the best information to maximize their timely access to clinical trials of targeted therapeutics. Guidance should also be provided for health emergencies and population lockdowns in order to optimize the use of resources and provide simplified procedures that do not affect a trial's quality or ethical principles.

ESMO papers and recommendations:

- [ESMO-EORTC position paper on the EU Clinical Trials Regulation and EMA's Transparency Policy: Making European research more competitive again \(https://www.annalsofncology.org/article/S0923-7534\(19\)31523-6/fulltext\)](https://www.annalsofncology.org/article/S0923-7534(19)31523-6/fulltext)
- [Beyond the lessons learned from the COVID-19 pandemic: opportunities to optimize clinical trial implementation in oncology \(https://www.esmooopen.com/article/S2059-7029\(21\)00198-8/fulltext\)](https://www.esmooopen.com/article/S2059-7029(21)00198-8/fulltext)

2. Protection and fostering of independent academic clinical research: Ensure an efficient legal framework for independent academic clinical trials that can optimize novel therapeutic multidisciplinary strategies and investigate important, but less commercially attractive, research areas and health issues. Increase independent funding mechanisms for independent academic clinical research, especially for international collaboration. Build upon existing guidelines to address collaboration between research groups and their appropriate interaction with the industry to clarify the roles and responsibilities of all partners involved in the clinical trials from the onset.

ESMO papers and recommendations:

- [Safeguarding the Future of Independent, Academic Clinical Cancer Research in Europe for the Benefit of Patients \(https://doi.org/10.1136/esmooopen-2017-000187\)](https://doi.org/10.1136/esmooopen-2017-000187)
- [Current models, challenges and best practices for work conducted between European academic cooperative groups and industry \(https://doi.org/10.1136/esmooopen-2019-000628\)](https://doi.org/10.1136/esmooopen-2019-000628)

3. Streamlining the clinical trials process: Simplify, decentralize, and reduce the bureaucratic requirements of clinical trials, which is especially challenging for non-commercial trials. It is crucial to ensure that if any guidelines or regulations are put in place to govern clinical trials, that they foster health research, high-quality data, and optimal healthcare practice, rather than obstruct them. They must be created in a forward-looking manner that does not impede advances in scientific research, and allows for the coordination of multi-centre and multi-country trials and the use of health data in a way that supports the medical field, without making it cumbersome for healthcare professionals, sponsors, and patients.

ESMO papers and recommendations:

- [ESMO Clinical Research Observatory \(ECRO\): improving the efficiency of clinical research through rationalisation of bureaucracy \(https://doi.org/10.1136/esmooopen-2019-000662\)](https://doi.org/10.1136/esmooopen-2019-000662)
- [Streamlining clinical research: An ESMO awareness call to improve Sponsoring and Monitoring of Clinical Trials \(https://www.annalsofncology.org/article/S0923-7534\(22\)04185-0/fulltext\)](https://www.annalsofncology.org/article/S0923-7534(22)04185-0/fulltext)

ESMO stands ready to collaborate with the WHO throughout the discussion process and offers to mobilise its network of medical oncologists, health professionals and researchers to support the design of robust and successful WHO guidance on clinical trials.

### Question 1

1. Does the above description capture critical elements of the clinical trials ecosystem?

Yes, the above description captures critical elements of the clinical trials ecosystem, but we would add the following:

- Strengthening the role of patients/patient advocates in the design, approval and reporting of clinical trials.
- Promotion of financial and organizational support of not-for-profit investigator-initiated clinical trials by the public and private sector.
- Representation of the physician/trialists in the ICH body developing and revising GCP guidance documents.

2. Which elements are incorrectly stated?

We do not feel that any of the elements are incorrectly stated.

3. Are you aware of existing up-to-date descriptions of the clinical trials ecosystem relevant to public, private, civil society organisations and philanthropic foundations and all WHO regions? If so, please provide references.

Please consult the ESMO webpage that provides information on not-for-profit cooperative oncology trial groups: <https://www.esmo.org/research/research-groups-tools-and-database>

### Question 2

*The resolution requests WHO to lead a consultation process to advance best practices and measures that strengthen the global clinical trials ecosystem. The resolution mentions International Council for Harmonization (ICH) explicitly.*

1. Are you aware of relevant initiatives besides ICH related to strengthening the global, regional, or national clinical trials ecosystems?

We are not aware of relevant initiatives besides ICH.

2. Are there adequate clinical trials networks/initiatives covering all WHO regions and all relevant population groups currently, or are they more or less needed?

Several clinical trial networks exist that bring together not-for-profit oncology cooperative groups, research groups, databases and tools. Please see the ESMO web page: <https://www.esmo.org/research/research-groups-tools-and-database>

In contrast, industry-sponsored trials are launched and promoted in dedicated platforms, with less cooperation between different industrial sponsors.

All clinical trials are required to be submitted in European and US trial registries (<https://eudract.ema.europa.eu/>, [www.clinicaltrials.gov](http://www.clinicaltrials.gov)).

3. How can capacity development for clinical trials networks in normal times which focus on endemic communicable or noncommunicable diseases best be related to preparations for future pandemics?

Rapid connection and integration of national/regional clinical trial networks in an international 'pandemic-grade' network requires: a) available legal/regulatory framework, b) agreement on data protection and sharing, c) homogeneous and streamlined clinical research guidelines and standard operating procedures, d) flexible and fast funding mechanisms, e) an international governance framework.

4. How best can mechanisms be put in place to trigger a pivot for activity of endemic disease networks towards pandemic response?

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5. What is the role of national vs international networks?

International networks are better positioned to develop clinical trial activities in a) rare cancers, b) molecularly-defined subgroups of common tumours, c) identification of modest treatment effects in patients with common tumours (large sample size required), d) representation of minorities and all ethnic/genetic groups in study populations for better extrapolation to real world conditions.

6. How can international networks best meet public health needs in each country they operate in?

Study and implementation of a validated balance between universal SOPs/frameworks and national realities/frameworks/disease epidemiologies and unmet needs should be pursued by means of multinational representation in trial authorization, scientific and data monitoring committees.

### Question 3

WHO's [R&D Blueprint](#) is a global strategy and preparedness plan that allows the rapid activation of R&D activities during epidemics. What additional steps can be taken to facilitate rapid implementation of agreed trial protocols during pandemics and epidemics?

Please see our answers to questions 2.3 and 2.4 above regarding the requirements for the rapid connection and integration of national/regional clinical trial networks in an international 'pandemic-grade' network.

### Question 4

With regard to the resolution text, What do you consider to be "the respective roles of the WHO Secretariat, Member States and non-State actors, [in] ... best practices and other measures to strengthen the global clinical trial ecosystem, taking into account relevant initiatives where appropriate"?

WHO can work together with national governments and international authorities, as well as non-state actors, for effective development of international framework agreements on a) legal/regulatory authorisation, b) data protection

and sharing, c) homogeneous and streamlined clinical research guidelines and standard operating procedures, d) flexible and fast funding mechanisms, e) international governance networks.

### Question 5

*The resolution is related to research waste through its focus on best practices for well-designed and well-implemented trials and its wording on preventing underpowered, poorly designed, or under-reported trials.*

We define research waste for the purpose of this question to be “any practice that does not allow outcomes of research to contribute to science or public health, including poorly designed, implemented or reported research studies”.

What are the best practices in reducing research waste, and what are the roles of WHO, Member States and non-State actors in implementing such best practices?

a) Empowering independent experts and their bodies, patient advocates and trial-approving authorities in the robust assessment of design and public health relevance of submitted clinical trial authorizations, b) allowing information sharing and joint decision-making processes between the above, so as to avoid trial duplications across countries, c) implement legal requirement for reporting of all completed or discontinued trials, d) link public funding of trials to accountability mechanisms for the monitoring and reporting of trials.

### Question 6

*The collection, management and sharing of clinical trial data in an ethical and secure manner is fundamental to the conduct and reporting of high quality clinical trials.*

Many agencies (including [WHO](#)) have implemented policies to support data management, sharing and reuse of clinical trials and other research datasets in order to advance science and public health.

What measures are needed (legal, technical, other) to ensure that fair and transparent processes are in place to enable access to and reuse of clinical trial datasets in a manner that is appropriate for diverse settings?

Legal requirements are currently foreseen in the [EU General Data Protection Regulation](#) (GDPR), [EU Clinical Trials Regulation](#) (CTR), ongoing regulations for the European Health Data Space (EHDS), and Artificial Intelligence (AI). Technical guidance relates mostly to standard, universal SOPs for clinical research and interoperable IT, Electronic Health Records (EHR) systems and common data models and data dictionaries.

### Question 7

What do you consider to be measures that can be taken to better utilize digitization and move towards paperless approaches to clinical trials whilst safeguarding subject protections and data quality, measures that are suitable for countries of varying income levels around the world?

Measures should be streamlined and implemented for the development/promotion of:

- Digital infrastructure
- Digital literacy
- Common data dictionaries
- Adherence to ICH practices for clinical research
- Interoperable, modular IT and EHR systems
- Consistent regulatory frameworks for digital health and digitized clinical trials, including data security
- Available funding mechanisms and incentives for digital infrastructures and for digitized clinical trials

### Question 8

What measures can be taken, and by whom, to address the insufficient representation of specific population segments in clinical trials, such as low income countries (LIC) and lower middle income countries (LMIC) populations, pregnant and lactating women, neonates, children, the elderly and the immunocompromised?

Clinical research infrastructure and technology transfer are needed for LMICs, along with incentives and funding mechanisms.

A multistakeholder approach should be implemented for in principle inclusion of elderly, immunocompromised patients in cancer clinical trials or for providing a robust scientific rationale for their exclusion. Stakeholders should be investigators, trial authorization bodies, ethics committees, patient associations.

Incentive schemes are needed to promote real world representativeness of trial populations and to implement the linkage of trial populations to restrictive authorisations/reimbursement of new therapies only in the populations under study.

### Question 9

What measures can promote clinical trials that address unmet needs in populations that have been neglected or underserved, such as those suffering [neglected tropical diseases](#), [rare diseases](#), the [WHO priority list of antibiotic-resistant bacteria](#) and the [WHO R&D blueprint priority list](#).

Rare Cancers urgently need collaboration and networking of national research groups, the implementation of novel trial and analysis methodologies, the development of regulatory incentives for research in rare cancers as well as of reimbursement incentives for rare cancer therapeutics.

### Question 10

What measures can be taken, and by whom, to ensure evidence generated from clinical trials is considered higher quality from the clinical guidelines perspective, given that ICH already provides guidance for submission of data to regulatory authorities?

We support the integration of 'Level of Evidence' ranking schemes in all recommendations present in clinical guidelines, under the responsibility of the producing society/body.

ESMO already implements this requirement, along with value scales, the [ESMO Magnitude of Clinical Benefit Scale \(ESMO-MCBS\)](https://www.esmo.org/guidelines/esmo-mcbs) (<https://www.esmo.org/guidelines/esmo-mcbs>) and actionability scales, the [ESMO Scale for Clinical Actionability of molecular Targets \(ESCAT\)](https://www.esmo.org/policy/esmo-scale-for-clinical-actionability-of-molecular-targets-escat) (<https://www.esmo.org/policy/esmo-scale-for-clinical-actionability-of-molecular-targets-escat>) in the [ESMO Clinical Practice Guidelines](https://www.esmo.org/guidelines) (<https://www.esmo.org/guidelines>)

Guidelines with such features should be prioritized for use/impact in HTA and reimbursement bodies and their decision-making processes.