Response to 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"

The George Institute for Global Health welcomes the opportunity to provide feedback on WHA resolution 75.8. Our key recommendations to improve the global clinical trials ecosystem are:

- **Ensure adequate and timely recruitment of participants to trials to meet sample size requirements**, so that studies can answer clinical questions and thus avoid waste. This requires access to large populations of diverse and representative participants, something which Member States and the WHO can support by establishing research registers and clinical trials networks, integrating trials into routine health care settings, and ensuring collaboration across regions.
- **Consolidate ethics practices across regions and develop better mechanisms for rapid approval**. Overly complex and obstructive ethics and governance practices limit the ability to rapidly recruit participants to trials and to collaborate across regions, contributing to waste. Member states and the WHO can support by simplifying and streamlining ethics practices.
- **Ensure participation in clinical trials from sites in rural, regional, remote, marginalised and resource-poor settings, and adequate representation of underserved populations** among both trial teams and participants. A lack of diversity in trial populations limits the broader applicability of trials and thus their ability to contribute to science and public health in a meaningful way. Non-State actors can support equitable participation and representation by identifying and engaging with collaborative partners, improving the accessibility of clinical trials, and providing appropriate support for participants to optimise retention.
- **Report on diversity in trial populations and inclusivity in recruitment** as a requirement of funding bodies and peer-reviewed journals. Member States, the WHO and non-State actors who fund or publish research can support this by making such a reporting requirement mandatory.
- **Ensure that trials focus on research questions and include research methods that reflect the priorities, culture, and needs of the communities they seek to serve.** Non-State actors can support this by developing frameworks and mechanisms to involve target groups in research, including community and consumer representation in governance structures. Member States and the WHO should invest in developing core outcome sets relevant to low- and middle-income countries (LMICs), to ensure that the right research questions are being addressed, and that clinical trials are not conducted when they are not needed to answer those questions.
- **Provide universal access to affordable and comprehensive training courses in clinical trial design and conduct.** As part of the funding and ethics approval processes, Member States and the WHO should require Chief Investigators, trial methodologists and operational teams to demonstrate competency in trial design as part of the submission process, via a Good Clinical Practice qualification or equivalent. Member States and the WHO should work with non-State actors to provide access to appropriate training courses to ensure this.
- **Ensure systematic and transparent registration and reporting of clinical trials.** Clinical trial registries should harmonise the data parameters they use for individual participant data availability (see https://pubmed.ncbi.nlm.nih.gov/36337374/). Poor reporting of the results of clinical trials should be addressed in order to facilitate evidence synthesis.

Question 1

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.

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

No

The description does not explicitly mention the need to ensure post-trial access to new interventions, or refer to issues related to the Intellectual Property (IP) generated and the need to waive IP rights in the event of a public health emergency.

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.

No

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.

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

Yes

The Aim of Accelerating Clinical Trials in the EU (ACT EU) initiative, launched by the European Commission (EC), the Heads of Medicines Agencies (HMA) and the European Medicines Agency (EMA) this year to transform clinical trials within the European Union (EU).

Accelerating Clinical Trials in the EU (ACT EU) initiative launch (europeanpharmaceuticalreview.com)

Accelerating Clinical Trials in the EU (ACT EU) (europa.eu)

The Indian Clinical Trial and Education Network (INTENT), an initiative to build a network of research institutes in India to provide evidence-based, robust and culturally sensitive solutions to urgent health problems, in a reasonable time frame, by conducting large multi-centric clinical trials.

Intent - Indian Clinical Trial And Education Network (INTENT) (icmr.org.in)

The Consolidated Standards of Reporting Trials (CONSORT) initiative (https://www.consort-statement.org)

The Clinical Trials Transformation Initiative (https://ctti-clinicaltrials.org)

The Australian Clinical Trial Alliance (https://clinicaltrialsalliance.org.au)

If so, please fill out the table below with the most appropriate recent initiatives that may be of relevance and should be considered by WHO in actions related to WHA 75.8

COMPLETE AS APPROPRIATE

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

There are adequate clinical trials networks in some regions, but more are needed to provide consistent coverage across all WHO regions and population groups, and ideally there would be a level of standardisation across these networks.

In the UK, the UKCRC Registered CTU Network (ukcrc-ctu.org.uk) fills this role, and in India, the Indian Council of Medical Research supports the Indian Clinical Trial and Education Network (INTENT - icmr.org.in). Efforts are underway to set up a similar network in Australia.

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

Capacity development for clinical trials networks can best serve to prepare for future pandemics by focusing on the health systems within which clinical trials are run. Health systems strengthening is essential both in and of itself, but also to ensure capacity for effective clinical trials during future pandemics and other public health emergencies. Key elements include good electronic health record systems and strong buy-in to clinical trials from physicians.

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

One key mechanism that could support a pivot towards pandemic response is the establishment of central ethics approval committees at the national level. These committees could address current delays in the approval of clinical trials resulting from a lack of capacity in some contexts.

Other mechanisms to consider include the development of a pandemic toolkit; the formation of national committees tasked with ensuring readiness to pivot clinical trials towards pandemic

response, including regular testing of systems and processes; and the preparation of waivers to assist in circumnavigating data protection legislation such as General Data Protection Regulation in the EU in order to facilitate a coordinated global response.

What is the role of national vs international networks?

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

International networks should have local representatives in the countries they operate in, who are able to adapt international/global 'guidance' on clinical trials to the national context. These representatives should work with appropriate partners to conduct environmental scans to identify key priorities and unmet needs.

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?

Establishing a global or centralised ethics review body should be considered during pandemics and epidemics, in order to expedite ethics approval processes. In addition, a central coordination mechanism could minimise duplication across multiple trials and therefore cut research waste.

See also responses to question 2.

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"?

Roles of the WHO Secretariat

Roles of Member States

Roles of non-State actors

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?

Best practices that can serve to reduce research waste include:

- **Ensuring adequate and timely recruitment of participants to trials to meet sample size requirements**, so that studies can answer clinical questions and thus avoid waste. This requires access to large populations of diverse and representative participants, something which Member

States and the WHO can support by establishing research registers and clinical trials networks, integrating trials into routine health care settings, and ensuring collaboration across regions.

- **Consolidating ethics practices across regions and developing better mechanisms for rapid approval**. Overly complex and obstructive ethics and governance practices limit the ability to rapidly recruit participants to trials and to collaborate across regions, contributing to waste. Member states and the WHO can support by simplifying and streamlining ethics practices.
- **Ensuring participation in clinical trials from sites in rural, regional, remote, marginalised and resource-poor settings, and adequate representation of underserved populations** among both trial teams and participants. A lack of diversity in trial populations limits the broader applicability of trials and thus their ability to contribute to science and public health in a meaningful way. Non-State actors can support equitable participation and representation by identifying and engaging with collaborative partners, improving the accessibility of clinical trials, and providing appropriate support for participants to optimise retention.
- **Reporting on diversity in trial populations and inclusivity in recruitment** as a requirement of funding bodies and peer-reviewed journals. Member States, the WHO and non-State actors who fund or publish research can support this by making such a reporting requirement mandatory.
- **Ensuring that trials focus on research questions and include research methods that reflect the priorities, culture, and needs of the communities they seek to serve.** Non-State actors can support this by developing frameworks and mechanisms to involve target groups in research, including community and consumer representation in governance structures. Member States and the WHO should invest in developing core outcome sets relevant to low- and middle-income countries (LMICs), to ensure that the right research questions are being addressed, and that clinical trials are not conducted when they are not needed to answer those questions.
- **Providing universal access to affordable and comprehensive training courses in clinical trial design and conduct.** As part of the funding and ethics approval processes, Member States and the WHO should require Chief Investigators, trial methodologists and operational teams to demonstrate competency in trial design as part of the submission process, via a Good Clinical Practice qualification or equivalent. Member States and the WHO should work with non-State actors to provide access to appropriate training courses to ensure this.
- **Ensuring systematic and transparent reporting of clinical trials.** Poor reporting of trial results can make it difficult to include them in evidence syntheses, limiting their contribution to science or public health. The WHO and Member States should require trial teams to report results in a systematic, standardised way to address this.

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?

Measures needed to enable access to, and reuse of, clinical trial datasets include:

- **Clear, well-designed participant information and consent documents that enable individuals to consent (or not) to their de-identified data being used for future research**. In some contexts,

the use of innovative methods of presenting participant information to patients will be needed; for example, the use of illustrations or videos.

- **Legal and technical systems that enable trial participants to prospectively consent to the secure secondary use of their data**. Secondary use of data for purposes other than the primary aim of a trial is important but often restricted. Processes to secure consent for the secondary use of data should be integrated broadly and welcomed by ethics departments.
- **Technical mechanisms to quarantine data where consent has not been provided, and legal mechanisms to support the sharing of data across regions and countries.**
- **Data governance structures and processes that include clinical trial participants.** Research data governance is an evolving space. Clinical trial participants may have a different perspective on how datasets should be used to that of trial regulators, who should ensure that trial participants are part of the decision-making process.

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 that can be taken to better utilize digitization include:

- **Investment in standardisation of the acceptance of digital consent, Case Report Forms (CRFs) and other clinical trials documents.** The COVID-19 pandemic has accelerated a paperless approach to clinical trials among many global groups, but in some contexts, this is not yet possible or considered desirable. Some governments continue to require documents such as Patient Reported Outcome Measures (PROMs) to be in paper form, and/or consent forms to have 'wet ink' signatures. **Equity of access to clinical trials must be a key consideration** as the digital landscape evolves in the coming years, and in low-resource contexts the WHO should consider providing the digital tools needed to take a paperless approach to clinical trials.
- **Access to standardised global online platforms that facilitate digital consent, CRFs and other documentation.** Currently some digital solutions for investigator-initiated research are prohibitively expensive. Researchers should have access to online platforms that can securely facilitate digital consent and risk-based monitoring without incurring exorbitant costs.
- **Implementation of the WHO's Global Carbon Reduction Guidelines, with investment in the infrastructure required in LMICs for implementation and advocacy.** The digitization of clinical trials can support achievement of environmental targets, and framing it in this way with governments may increase support for a move to paperless approaches. The use of digital devices rather than printing hard copies of documents can help to reduce deforestation.

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?

- **Research regulators** should stipulate that trials should not exclude pregnant women unless there is a valid, a priori reason to do so. They should also require that specific approval is sought by investigators who do not plan to include equal percentages of women and men in their trial, with reasonable justification for this decision. Finally, they should require investigators to

demonstrate how they have considered the profile of their trial population and will ensure diversity of participants in terms of race, ethnicity, age, socio-economic status etc.

- **Research ethics committees** should have a diverse membership that reflects the population and representation targets for trial participants, including a diversity of demographic characteristics in terms of age, gender, race, ethnicity, sexuality etc. Committees should also include members with relevant lived experience.
- **Research funders** must mandate that studies a priori aim to recruit a diverse, representative population, embedding this in the trial protocol, and that they report on the diversity of their study populations.
- **Peer review journals** must also demand that authors/ investigators report on the diversity of their study population. Studies that are not representative (without reasonable justification) should not be accepted for publication.
- **The WHO and clinical trials networks** should advocate for the informed and safe inclusion of pregnant and lactating women and other historically excluded populations in clinical trials. They should also work with researchers, governments and other partners to implement community education campaigns to increase awareness, clinical trials literacy and participation.

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?

Researchers should build equitable relationships with neglected and underserved populations and establish frameworks and mechanisms to involve them in research, including community and consumer representation in governance structures. This can help to ensure trials focus on research questions and include research methods that reflect the priorities, culture, and needs of the communities they seek to serve.

Research funders including governments and the WHO can support this by mandating such mechanisms in the application process, and by funding PhD and post-PhD retention programs focused on addressing unmet needs, to build research capacity in these areas.

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?

A more systematic process of registering trial results outside of the peer-reviewed literature should be considered, with a 'grading' applied to indicate the quality of the trial in each case.

See also suggested 'best practice' in clinical trials, set out in response to question five.

Question 11

When global research priorities have been agreed, there has been variable success in coordinating funding from research funding agencies to ensure agreed priorities are supported efficiently.

How can research funding agencies work more effectively together, particularly during epidemics and pandemics?

Global governance structures should be established to support collaboration and coordination across research funding agencies.

And how best can funding address the inequities in current resource allocations to LIC and LMICs?

Targeted calls and research funding quotas for different contexts should be agreed and implemented to address the inequities in current allocations.

Question 12

ICH is not explored in question 12, given that ICH has a central role concerning National Regulatory Authority (NRA) submissions of clinical data.

Other than ICH, what critical initiatives relate to the resolution and may already have articulated best practices and clinical trials ecosystems, as framed by the resolution?

For example, what is your perspective on clinical trials and the CIOMS Working Group report on clinical research in resource-limited settings?

What is your view of the Good Clinical Trials Collaborative guidance?

Question 13

WHO International Clinical Trials Registry Platform (ICTRP)

Given very limited resources, what should be the key priority for improving the ICTRP database, Search Portal, and Registry Network to adequately support the clinical trials ecosystem?

How can quality of registration data best be improved at both the source registry level and the ICTRP level to support the aims of the resolution?

The WHO should engage with source registries to ensure that data fields and their subfields for availability of data for Individual Participant Data (IPD) meta-analysis are in alignment with International Committee of Medical Journal Editors (ICMJE) standards, which enable evidence synthesis and, ultimately, quicker development of the evidence base. An audit found that only 4 (22.22%) registries from which the WHO sourced data were aligned with the standards (see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9635347/).

Question 14

The WHO Global Observatory on Health R&D (Observatory) currently provides visualizations of clinical trials globally based on the ICTRP database.

What measures can be taken to improve visualizations in the Observatory?

Question 15

How can the ecosystem lead to efficient adaptation and deployment of capacities during Public Health Emergencies of International Concern (PHEIC)? Please offer examples of best practices and lessons learned.

What do you consider best practices of expedited procedures for rapidly implementing clinical trials in PHEIC that meet regulatory and ethics oversight?

Question 16

If you have any comments, lessons learned, gaps or bottlenecks relating to the clinical trials ecosystem you would like to share, which are not addressed in the previous questions, please provide them here