The future of the global clinical trial ecosystem: a vision from the first WHO Global Clinical Trials Forum

Published Online
December 18, 2023
https://doi.org/10.1016/
S0140-6736(23)02798-8

The first WHO Global Clinical Trials Forum[1] held at WHO, Geneva, Switzerland, on Nov 20–21, 2023, brought together a diverse community to advance sustainable global clinical trial infrastructure. To secure the improvements needed to "strengthen clinical trials", as mandated by the World Health Assembly in May, 2022,[2] the Forum agreed a unified vision of "always on, always busy", whereby sustained national and global clinical trial capacity during and between crises ensures clinical research and trials are integrated and sustained in all health systems so that trials can help improve health outcomes for all, all the time.

The infrastructure and action needed to develop this global vision must be built and sustained now, and kept functional through trials that answer the most important questions that patients, participants, and clinicians face. This system needs to be equitably embedded into research-oriented health systems that allow for improvements to clinical practice to be continuously updated in the course of clinical management. To ensure equity, broad-based capacities should be available globally to coordinate and lead large-scale, high-impact trials that improve clinical care and disease prevention. Trial infrastructure should ensure health workers can participate in their local languages in national, regional, and international multicentre clinical trials. This proposed approach to infrastructure and sustained support would allow trials to be functional and used all the time and would avoid the inefficiencies of starting up and ending projects with loss of expertise and human capacity.

Patient and community engagement is central to the vision since trials must start with patient and community needs, ensure these perspectives are integrated through the design and implementation, and that results are communicated promptly to patients and communities. Although trust in science has been challenged during the COVID-19 pandemic, the interest in participating in trials and communities using evidence to inform decisions from well conducted trials has been strengthened.[3] The vision set out by the WHO Global Clinical Trials Forum seeks to improve trust by placing patient and community engagement at the heart of clinical trials, with diversity, equity, and inclusive approaches. Trialists, funders, communities, and organisations in the Global South should share an equal leadership role for prioritisation, trial design, and analyses and increasingly invest domestic resources as feasible and appropriate to support sustained national clinical research infrastructure as part of routine health services. Given the global rise in non-communicable diseases,[4] including cancer, cardiovascular diseases, neurological disorders, and mental illness, in many low-income and middle-income countries, future national and global health trials must address both infectious and non-infectious diseases.

There was consensus that clinical trial approval procedures require urgent reform. The discussion at the Forum included the four broad pillars that support the clinical trial ecosystem in each country (figure); human resources and career opportunities for clinical researchers with institutional clinical trials infrastructure and capabilities; national policy and legal frameworks for clinical trials, including registration and financing; regulatory systems; and research ethics systems.

Building on these pillars, key recommendations for strengthening trials included the following actions. Those engaged in trials must first ensure optimal scientific and ethical design, by focusing on questions that are relevant to diverse patients and communities and making sure pivotal aspects such as sample size, populations, outcomes, and intervention design are appropriate; the Good Clinical Trials Collaborative's Guidance sets out relevant criteria in this regard.[5] Quality should be by design. Evidence suggests enormous research waste during the COVID-19 pandemic[6,7] through the conduct of many small, generally investigator-initiated trials with poor design. This wasteful approach must stop so that

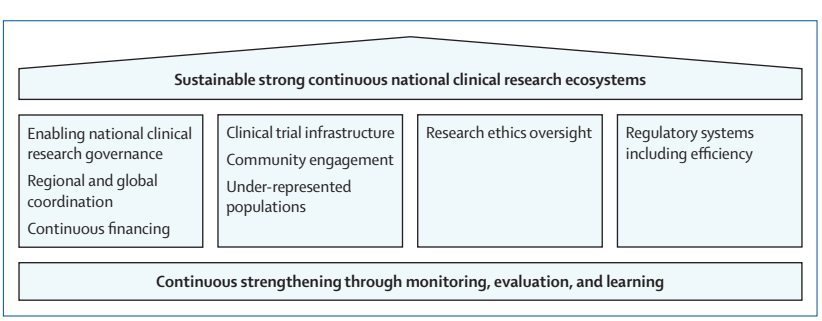

Figure: **Four broad pillars supporting the clinical trial ecosystem**

patients and resources are included in trials that can contribute through well designed trials to improving evidence-based medicine. Furthermore, there is scope for greater innovation in the methodological aspects and operational conduct of trials embedded in large national and international platforms. These innovations can allow for greater efficiency in design such as that achieved through adaptive trials[8,9] and remain pertinent both during and between crises.

Second, those engaged in trials should use best practices for well designed and well implemented trials,[10] including greater use of digital technologies and a more risk-proportionate approach to trial monitoring and oversight. This includes improvements in the application of statistical methods to trials, notably for sample size calculations linked to credible estimates of event rates and effect sizes. Thousands of trials each year do not involve investigational products and are out of scope for the existing International Council for Harmonisation Good Clinical Practice (ICH-GCP) guidance.[11] Upcoming WHO best practice interventional clinical trials guidelines, which are currently out for consultation and are expected to be finalised in 2024,[10] will clarify approaches for evaluating existing intervention optimisation and minimising research waste. Consequently, there is great scope to enable evidence generation by focusing resources on the key features of well designed and well implemented trials; accelerating timelines to ensure faster uptake of proven interventions that save lives and stopping the use of interventions that do not work or cause harm; and reducing costs. The outcome should be fewer, better trials that are fit for purpose, and risk-proportionate authorisation and monitoring processes that enable these well designed trials to be approved quickly through a minimum number of necessary approval steps.

Third, to enable monitoring of capacity development progress towards a sustainable global trial infrastructure, a maturity framework for the clinical trial ecosystem should be developed based on the elements of best practices specified in the WHO guidance that is close to finalisation.[10] For the maturity framework it will be desirable to build on existing self-assessment maturity tools for national regulatory systems and ethics oversight[11,12] by establishing a clinical trial unit global maturity framework to support capacity development in this area.

For more on **AVAREF** see https://www.afro.who.int/health-topics/immunization/avaref

One barrier that needs to be overcome is how best to implement agreed guidance on improving design. There are key scientific and ethical considerations outlined in the draft guideline ICH E6 R3, guideline ICH E8 R1, and the draft WHO guidance;[10,11,13] these guidelines are aligned. There is a need for broad-based training in relation to these design considerations and WHO plans to coordinate with key clinical trial stakeholders to develop training materials. There are actions for funders, regulators, ethics authorities, and researchers in improving the design and implementation of trials.

A second barrier to be overcome is the need for much greater integration of clinical trials into health-care systems to better link researchers with health-care practitioners. This integration requires embedding research staff into health system facilities, such as in the UK National Institute for Health and Care Research (NIHR) model, whereby research nurses are trained and closely linked to the national health system.

Efforts also need to be made to harness the support of a small number of large international clinical research networks per region and disease area. This approach could lead to an interconnected ecosystem with large, functional, ongoing clinical trials integrated into health systems around the world, continuously improving the evidence base and answering questions that are directly relevant to patients and clinicians. These networks should maximise inclusion of under-represented populations as a standard practice, such as children, pregnant and lactating women, and older people.

Finally, national ecosystems should keep track of inefficiencies and monitor ways to improve them, for example through single Institutional Review Board and Research Ethics Committee models, ensuring parallel rather than sequential regulatory and ethics review, single submission systems for registration, regulatory and ethics review for multicentre studies, enabling importation of investigational products for key trials, and developing master clinical trials agreements to reduce the existing contracting delays. For international trials, coordination and streamlining between authorities must become the norm. AVAREF (the African Vaccine Regulatory Forum) was highlighted as a functional model that delivers timely multi-country review that has been monitored and shown to reduce timelines while safeguarding standards.[14]

The advent of the randomised controlled trial, coming broadly into use in the second half of the 20th century,

is one of the most impactful innovations in public health, enabling decisions on use of interventions to be made on sound evidence. Over the past few decades the global clinical trial ecosystem has gained in complexity and in cost and lost efficiency, while capacity development has stalled in many places. The global clinical trial community is now at an inflexion point. Failure to act now risks decades of slow progress. Responding to the recommendations for reforms identified by the first WHO Global Clinical Trials Forum will ensure we redevelop a system fit for purpose at global, regional, and national levels with roles for funders, researchers, regulators, ethicists, clinicians, and, crucially, research participants, patients, and communities in a transformed global clinical trial ecosystem.

We all took part in the WHO Global Clinical Trials Forum discussed in this Comment and VM, WZ, JR, and JF report grants from EDCTP, the UK National Institute for Health Research (NIHR), and the Bill & Melinda Gates Foundation related to this forum. IA reports support from NIHR (NF-SI-0616–10037 and RP-PG-0217-20009) and the European Union under grant agreement N. 101046314. WHO acknowledges input from the many participants in the global and regional consultations on strengthening clinical trials that have occurred during 2023. The global forum was supported by funds from the Bill & Melinda Gates Foundation (INV-064296). The regional consultations leading into the global forum and WHO normative guidance development have been funded as part of the EDCTP2 programme supported by the European Union (grant number CSA2023WHO-3454-WHORCT) with funds from the UK NIHR using UK aid from the UK Government to support global health research. The views expressed in this Comment are those of the authors and not necessarily those of WHO, the Bill & Melinda Gates Foundation, EDCTP, the NIHR, the UK Department of Health and Social Care, the European Union, or the European Health and Digital Executive Agency.

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