

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

1. In May 2022, the Seventy-fifth World Health Assembly recalled Health Assembly resolutions dating back to 2005,¹ noted the recommendations made by the Independent Panel for Pandemic Preparedness and Response in their review “COVID-19: make it the last pandemic”² relating to health research and development, including clinical trials, and adopted resolution WHA75.8 *Strengthening clinical trials³ to provide high-quality evidence on health interventions and to improve research quality and coordination⁴*.
2. In resolution 75.8, Member States⁵ recognized that “well-designed⁶ and well-implemented clinical trials are indispensable for assessing the safety and efficacy of health interventions” and acknowledged “the importance of promoting equity in clinical trial capability”. In seeking to improve the quality of evidence generated in clinical trials and their coordination, WHA 75.8 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.
3. While 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, this report addresses the efforts made to date to implement the requests made to the WHO Director-General in WHA75.8.
4. This report is being provided to supplement the Director-General’s report to the Health Assembly, submitted through the 152nd session of the WHO Executive Board, on the implementation of resolution WHA75.8 (document EB 152/13) published on 16 December 2022.⁷

¹ Including: WHA58.34 (2005) acknowledging that high-quality, ethical research and the generation and application of knowledge are critical in achieving internationally agreed health-related development goals, WHA63.21 (2010) outlining WHO’s role and responsibilities in health research, WHA66.22 (2013) and WHA69.23 (2016) on the follow-up of the report of the Consultative Expert Working Group on Research and Development: Financing and Coordination, WHA67.20 (2014) on regulatory system strengthening for medical products, WHA67.23 (2014) on health intervention and technology assessment in support of universal health coverage, WHA74.6 (2021) on strengthening local production of medicines and other health technologies to improve access, and WHA74.7 (2021) on strengthening WHO preparedness for and response to health emergencies.

² Independent Panel for Pandemic Preparedness and Response. COVID-19: make it the last pandemic, 2021 (https://theindependentpanel.org/wp-content/uploads/2021/05/COVID-19-Make-it-the-Last-Pandemic_final.pdf, accessed 11 December 2022).

³ “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).

⁴ Available at https://apps.who.int/gb/ebwha/pdf_files/WHA75/A75_R8-en.pdf (accessed on 10 December 2022)

⁵ And, where applicable, regional economic integration organizations.

⁶ 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.

⁷ Available at https://apps.who.int/gb/ebwha/pdf_files/EB152/B152_13-en.pdf (accessed on 23 December 2022).

IMPLEMENTING RESOLUTION WHA75.8

5. In resolution WHA75.8 the Health Assembly made a number of requests to the Director-General, as summarized in Table 1 below.

Table 1: Requests to the WHO Director-General adopted in resolution WHA 75.8

Area of work	Specific language from resolution WHA 75.8	Status
Consult with stakeholders, including Member States and non-State actors (in line with FENSA)	Organize, in a transparent manner, stakeholder consultations, in line with the Framework of Engagement with Non-State Actors (FENSA), 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	First round of consultations (written and in person) completed.
Review existing guidance and develop new guidance	Review existing guidance and develop, following the standard WHO processes, new guidance as needed on best practices for clinical trials, including on strengthening the infrastructure needed for clinical trials, to be applied in normal times and with provisions for application during a public health emergency of international concern, taking into account relevant initiatives and guidelines as appropriate, such as those led by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and other organizations	Initial review of existing guidance completed; secretariat in process of developing new technical guidance taking into account existing initiatives including ICH and other initiatives. This will follow standard WHO processes with external advisory group and draft planned for public consultation during 2023.
Provide guidance to Member States	Provide, as appropriate, guidance on best practices to help to guide Member States' implementation of scientifically and ethically sound clinical trials within their national and regional contexts	Support to Member States based on existing guidance is provided on request; this will continue and improve as new guidance is developed
Provide guidance to non-State actors	Provide, as appropriate, guidance on best practices for non-State actors in the design and conduct of clinical trials and in strengthening the global clinical trial ecosystem to meet the needs of major population groups that the intervention is intended to benefit, with a particular focus on under-represented populations, developed in consultation with Member States and relevant non-State actors	Guidance in development
Provide guidance to Member States	Provide to Member States, on their request, guidance, taking into account relevant initiatives and guidelines, as appropriate, on best practices for developing the legislation, infrastructure and capabilities required for clinical trials, taking into account national and regional contexts	Support to Member States based on existing guidance is provided on request; this will continue and improve as new guidance is developed
Engage with non-State actors	Engage with, as appropriate, relevant non-State actors in line with FENSA to strengthen clinical trial capabilities, particularly in developing countries, on innovations that meet the needs of major	Interactions ongoing, as appropriate, in line with FENSA

	population groups that the intervention is intended to benefit, with a particular focus on under-represented populations	
Report on progress in implementing WHA 75.8	Present a substantive report outlining progress in the activities requested of the Director-General in this resolution for consideration by the Seventy-sixth World Health Assembly in 2023 through the Executive Board at its 152nd session	Completed, with this report as an annex. We anticipate the the new guidance requested will be available by WHA 77 following standard WHO processes, and not by WHA 76.

6. This report focuses on enhancing and expanding on the information available in the Director-General's report on the stakeholder consultations held by WHO, with the aim of ensuring that the perspectives collected are accessible and can inform Member State guidance on the next steps.

7. While not the focus of this report, it is important to note that the WHO Secretariat has initiated, following standard WHO processes, the development of new guidance for clinical trials quality and ecosystem strengthening. An internal steering group has been constituted for this, as requested in resolution WHA75.8 (2022). A draft of the new guidance should be available for consultation with stakeholders by late 2023. As a starting point, 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 good randomized clinical trials² and; recent literature on clinical trials methods. In order to support Member States in strengthening their regulatory system(s), as urged in resolution WHA67.20 (2014) on regulatory system strengthening of medical products, WHO and Member States use a Global Benchmarking Tool for Evaluation of National Regulatory System of Medical Products.³ In addition, to help build capacity for the ethics oversight of research, WHO published in October 2022 a draft version of a WHO tool for benchmarking ethics oversight of health-related research with human participants.⁴ The Secretariat is proceeding with the rapid development of guidance and will update WHO's governing bodies regularly. As the Secretariat develops the guidance requested in resolution WHA75.8 (2022), it intends to develop a self-assessment tool with indicators for the maturity of the clinical trial ecosystem at national and international levels, aligned with and based on the wording of the resolution. A summary of clinical trials related indicators of maturity of Member States' regulatory systems based on formal benchmarking conducted by the WHO regulatory system strengthening team using the Global Benchmarking Tool for Evaluation of National Regulatory System of Medical Products has been published on the WHA 75.8 website as a baseline⁵.

IMPLEMENTING THE STAKEHOLDER CONSULTATIONS REQUESTED IN RESOLUTION WHA 75.8

¹ CIOMS. Clinical research in resource-limited settings: a consensus by a CIOMS working group. Geneva: Council for International Organizations for Medical Sciences; 2021 (<https://cioms.ch/publications/product/clinical-research-in-low-resource-settings>, accessed 17 December 2022).

² [The Good Clinical Trials Collaborative](https://www.goodtrials.org/): new proportionate guidance for Randomized Controlled Trials (RCTs) (www.goodtrials.org, accessed 10 November 2022).

³ 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).

⁴ WHO tool for benchmarking ethics oversight of health-related research with human participants. Geneva: World Health Organization; 2022 [website] (<https://www.who.int/publications/m/item/who-tool-for-benchmarking-ethics-oversight-of-health-related-research-with-human-participants>, accessed 10 December 2022).

⁵ <https://www.who.int/our-work/science-division/research-for-health/implementation-of-the-resolution-on-clinical-trials>

10. In 2022, the WHO Secretariat initiated its response to the request to transparently organize stakeholder consultations on the respective roles of the WHO Secretariat, Member States and non-State actors in developing guidance, identifying best practice and supporting capacity development – particularly in low- and middle-income countries. These consultations were designed to collect as much input as possible, to forward the substantive request that WHO “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”.

11. To stimulate stakeholder thinking and to help organize discussion, a document that framed questions was circulated in August 2022 to all technical departments in the WHO Secretariat to gather reactions and suggestions. Following this, the Secretariat arranged an internal coordination meeting on implementing resolution WHA75.8 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 in their respective networks to submit the inputs that they wanted to be included on major issues.

12. From 12 October 2022 to 11 November 2022, a public consultation page was opened on the WHO website to receive written inputs and comments from Member States and non-State actors. The page included the final framing questions.¹ To encourage as broad response as possible, the Secretariat held a consultation for Member States on 6 October 2022 and one for non-State actors on 7 October 2022, both focused on introducing the online consultation and on listening and discussing what improvements are needed to meet the resolution’s request to “identify best practices and other measures to strengthen the global clinical trial ecosystem”.

13. Over the course of the WHA 75.8 online consultation period (i.e., October to November 2022), 273 inputs were received, of which 53 were from Member States, including government agencies from the health and non-health sectors, and 63 were from non-State actors. Where WHO has received permission to make the full responses public, they will be made available on the WHA 75.8 website. The responses have been summarized and collated below.

RESPONSES RECEIVED AS PART OF THE STAKEHOLDER CONSULTATION²

1) Perspectives on the clinical trials ecosystem:

WHA 75.8 requests that WHO develop “guidance on best practices for design and conduct of clinical trials, including strengthening the global clinical trials ecosystem to meet the needs of the major population groups that the intervention is intended to benefit”. Inputs suggested that there are considerations for strengthening beyond the narrower definition of the ecosystem. The clinical trials ecosystem includes elements to prioritize, fund, 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. Inputs received highlighted the importance of patient, public and community involvement in research priorities, trial design, implementation and results reporting. Inputs also highlighted the importance of better liaison with bodies assessing the results, including regulatory authorities responsible for marketing authorization, research ethics committees, health technology assessment authorities and Member State authorities responsible for price and reimbursement decisions. Other inputs highlighted the importance of interaction with and learning from evidence review bodies responsible for guidelines and recommendations on clinical practice and public health. This includes systematic reviews and meta-analyses. It was highlighted that clinical trials are important for evaluation of non-pharmacological interventions such as behavioral interventions, and so strengthening of the clinical trials ecosystem should bear in mind the needs for clinical trials that do not include medical products.

¹ Available at https://cdn.who.int/media/docs/default-source/research-for-health/wha-75-8-stakeholder-consultation-framing-questions_fordownload.pdf?sfvrsn=e55c9641_3 (accessed on 15 December 2022)

² The views expressed in this report are those of the submitters. Nothing in this report should be construed or represented as the recommendations, position or policy of WHO.

Some respondents highlighted that clinical trials are different in normal times and emergencies, and therefore ecosystem needs should be considered differently.

The following sections group responses into high level categories of the ecosystem.

2) Perspectives on the strengthening needs for clinical trials capacity (personnel and infrastructure) particularly in low- and middle-income countries, including trial networks:

The inputs highlighted the key priority of further strengthening capacity in terms of both personnel and infrastructure to conduct high quality trials in low and middle income countries. It was recognized that the lack of capacity represents an ongoing gap in generation of evidence for priority health concerns in normal times, as well as a key risk in preparedness for future emergencies, as locally available capacities are indispensable in times of health emergency to generate evidence.

Respondents noted that some capacities and networks have already been expanded in a number of ways. The collation of networks and initiatives identified through the consultation are available at this website¹. Networks were identified in a number of thematic or disease areas but it was documented that these mostly focus on high income countries, with the exception of the AFRO region, where a number of networks have been supported working mostly on infectious diseases and maternal and child health. International networks are generally lacking in Latin America, the Caribbean, the WHO EMRO region and much of Asia. In many thematic or population group specific areas such as Antimicrobial resistance (AMR), paediatric trials, cancer trials, chronic neurological conditions and rare diseases the networks are overwhelmingly in higher income countries. It was noted that there is a major need to support capacity development in regions and countries that are currently under-represented. Major gaps in trial capacities and networks were identified in noncommunicable diseases (including cancer, diabetes, stroke, ischaemic heart disease and other chronic diseases) in lower-middle income countries, where these conditions are among the leading causes of death. There are networks that exist for specific disease areas in lower income countries, for example for some of the WHO list of Neglected Tropical Diseases, for HIV, malaria, tuberculosis and for maternal, neonatal and child health. However, gaps in networks remain even in these disease areas, most notably in Latin America, the Caribbean, the EMRO region and parts of Asia. There are successful initiatives in Africa, where sustainability is an important consideration. For example, the first and second programmes of the European and Developing Countries Clinical Trials Partnership (EDCTP) was highlighted as a successful initiative which has developed capacities and supported local leadership in many African countries. EDCTP clinical trials related grants include 44 African countries (including all French and Portuguese speaking countries in Africa), with major investments in clinical trial projects, capacity development initiatives that include subregional networks and personal fellowships and a specific focus on supporting generation of evidence for policy change by WHO and other bodies. EDCTP 1 & 2 has supported locally led capacity development, and there are lessons to be learned for capacity development initiatives in health. There are many other successful initiatives highlighted by the replies including those led by a number of government agencies, the European Commission and the Wellcome Trust. Taken together these confirm that high quality trials can be and have been conducted in very many settings around the world, but that major gaps remain in capacities. Guidances for equitable partnerships in capacity development were highlighted as a core consideration going forwards².

Long-term support to develop institutional capacity in lower and middle income settings is one aspect that some respondents indicated does not receive enough attention. Only through developing institutions can country ownership be supported, so that local and contextual factors become embedded in trial practice in ways that

¹ <https://www.who.int/our-work/science-division/research-for-health/implementation-of-the-resolution-on-clinical-trials>

² www.ukcdr.org.uk/resource/ukcdr-and-essence-2022-four-approaches-to-supporting-equitable-research-partnerships/

enable sustainability and build trust in communities that is needed for clinical trials to be successful. These are enablers for awareness and education of the general public and patients. Legal frameworks with provisions for clinical trial approval and medical product authorization are also essential aspects of capacity development.

There were distinct roles identified for national and international networks. National networks are best placed to understand national health priorities, workforce capability and links with the health system and enable patient and community engagement for clinical trials. They are also best placed to link with the regulatory bodies in the country. International networks may best function by incorporating a number of national networks in ways that allow for local and contextual factors to be taken into account appropriately. International networks that do not work adequately with national ones may not best support country ownership of research capacities. There are therefore best practices in how international networks interact with and support local and national capacities. Several respondents highlighted the importance and beneficial role of large scale clinical trials networks; other inputs highlighted that further work is needed to understand how such networks can best interact with and support local priorities. One successful model that was highlighted is that of the WHO Solidarity trial where Ministries of Health mobilized national networks, with close links to the health system, and with local leadership. The many networks will need to coordinate with each other, and the current gaps in such coordination mechanisms were highlighted as an area for further priority work. There is a need for more explicit inclusion of patients and community members in development and implementation for clinical trials, while ensuring that the needs and perspectives of trial participants are held at the forefront of capacity development activities.

Several respondents identified the importance of maintaining a focus on quality while seeking to reduce any unnecessary burden on researchers, which can prevent high quality trials from occurring, or delay them unnecessarily. Several respondents noted that progress with digital and mobile data collection, decentralized trials and the potential for health workers to be trained in data collection and embed trials into different levels of the health system, as well as expansion of telemedicine, are all opportunities for innovation to be built into capacity development. The importance of identifying the most locally relevant questions for clinical trials was highlighted, with discussions between researchers and policymakers earlier in trial design. The Clinical Trials Transformation Initiative and the Good Clinical Trials Collaborative are two initiatives that were highlighted as including useful guidance on quality and design of clinical trials.

Respondents indicated that commercial and non-commercial trial sponsors have distinct roles in the clinical trials ecosystem with slightly different objectives. Privately funded and conducted clinical research has a particular focus on generation of data that will prove acceptable to regulatory bodies for decision-making and potential marketing authorisation of medical products.

It was noted that a key learning from COVID-19 is that not enough is being done to ensure that resources are focused on good clinical trials, where capacities are developed, and not wasted on trials that prove uninformative. A set of actions need to be developed to direct public resources (both infrastructure and personnel) towards well-designed and well-implemented trials that generate evidence that can inform decision-making. Incentive structures and metrics for success need reform in this regard. Some respondents indicated that policy change or incorporation in guidelines/recommendations should be considered as a metric of success for public funding of clinical trials, and counting numbers of clinical trials may not be a good metric of success given the numbers of uninformative trials that were initiated during the pandemic.

Many respondents highlighted that clinical trial capacities are only functional if they are kept “warm” by ongoing research activities. It was highlighted that resources for capacities need to be matched with ongoing research activities.

With regard to data sharing, the need to create an enabling environment for data-sharing was highlighted, in which sharing clinical trial data does not add to the already high administrative burden on trialists. Creating such an environment requires specific additional resources, infrastructure, training and policies to promote ethical, equitable and efficient sharing of high-quality data, in compliance with applicable laws and regulations. In 2022, WHO published guidance in the area of research data sharing¹.

2) Perspectives on regulatory and research ethics committee capacity development and harmonization:

While there are ongoing initiatives to fund and support clinical trial capabilities, there are fewer initiatives that explicitly seek to fund and support national regulatory authority (NRA), other relevant national health authorities, and research ethics committee (REC) capacities. However, these are a core aspect of the clinical trials ecosystem for both publicly and privately funded and sponsored clinical trials and they require their own funding and support as a priority. The maturity of the ecosystem cannot progress without support to NRAs, other relevant health authorities and RECs. It is notable that while a great deal of funding was provided for conduct of clinical trials during the pandemic, less was provided to NRA, health authorities and REC strengthening at a time when the burden on these bodies was very great. At lower capacity levels, initiation of appropriately constituted and trained NRAs and RECs are a key need in the area of clinical trials approval. At higher capacity levels, coordination between NRAs, relevant national authorities, and between the many RECs required to approve a multi-site trial is a key area where activities are needed to improve efficiencies in the approval processes. Progress has been made with national coordination mechanisms in some countries, and with international coordination in some regions. For example a number of coordination fora have been utilized or established in the European region during the pandemic such as the Trials Coordination Board. Some respondents noted trends towards greater support for the following themes for functioning of NRA and REC oversight of clinical trials: embedding a risk proportionate approach to clinical trials; promoting patient and public involvement; improving inclusion and diversity of participants; and streamlining clinical trial approvals. Joint or coordinated parallel review between NRAs and REC can streamline procedures and avoid contradictory requests from different approval bodies, which should be avoided. There were calls to move away from sequential reviews to parallel processes. One aspect of oversight is ensuring that trials are prospectively registered in an appropriate clinical trial registry, that results are communicated to participants and disseminated to the scientific community and decision-makers. Examples of good practices in this regard were provided. Further work is needed to improve the way information is communicated, including through consent forms, in easily digestible ways, and public involvement in the trial oversight process can assist in this regard.

Most respondents highlighted the need for streamlining and harmonization of regulatory and ethical approval procedures. Some fora exist for coordination and potential harmonization of procedures. Respondents noted the helpful role of ICMRA (International Coalition of Medicines Regulatory Authorities), AVAREF (African Vaccine Regulators Forum), and in the UK the coordination between the Health Research Authority and the Medicines and Healthcare products Regulatory Agency. ACT EU (Accelerating Clinical Trials in the EU) aims to enable large, international trials. In some cases, large international, commercially sponsored trials are necessary to generate data for licensure of medical products. The private sector highlighted the successful example of ICMRA facilitating the alignment of regulatory expectations for first-in-human trials to speed up development of vaccines and therapeutics. Calls for regulatory harmonization are equally strong from the private and public sector respondents to the online consultation. It was notable that a very large scale trial (RECOVERY) was able to be initiated very quickly in the UK during the pandemic; the existence of prioritization and coordination

¹ <https://www.who.int/publications/i/item/9789240044968>

mechanisms between sites, and within and between approval bodies are necessary to allow for such large-scale rapid initiation.

Regulatory and ethical trial approval mechanisms will need to keep pace with developments in innovative trial design, discussed elsewhere in this document, so as to best enable improvements in trial practice while maintaining participant protections.

3) Perspectives on procedures for pivoting clinical trials capacities from normal times to emergencies:

Many respondents stated that the ability to pivot from ongoing work in normal times to rapid implementation of protocols in emergencies is critical, and this area needs further work. Multiple examples were provided of expedited procedures for approvals during the COVID-19 pandemic, and these represent a basis for further developing written procedures to expedite approvals in future emergencies. This remains a current gap ie the existence of written procedures to expedite approvals in all countries during emergencies. This is an urgent area of work for NRA, other relevant national health authority and REC strengthening activities in the area of pivoting from normal times to emergencies.

A key aspect of this needed work is expansion of country owned clinical research capacity which can address compelling use cases in normal times while being prepared to pivot in times of emergency. Some respondents indicated that funding models for clinical trial sites should support the concept of their engagement for multiple use cases. For example, clinical research capabilities can also support surveillance and data collection for epidemiological studies and burden of disease in local populations, which can be re-purposed for clinical trials as needed. Only capabilities which are kept functional by trials running in normal times will be available in times of emergencies. Therefore funders and governments should recognize that ongoing trials in normal times are developing and maintaining capabilities for future emergencies. This gives an additional rationale for resourcing of sites, networks and trials in normal times beyond the endemic use cases themselves.

Development of laboratory capacities should be planned in such a way that they can be applicable for a variety of purposes including for the laboratory aspects of trials. A holistic perspective was that even routine health information systems provide critical data to enable better surveillance (including detection of emerging pathogens) and these systems can provide more accurate baseline data to interpret potential adverse events in the context of trials. By recognizing the link between capacities in normal times and emergencies it may be possible to avoid the cycles of crisis followed by neglect in capacity development that have been seen in the past. Respondents supported the concept that trial networks should be funded to design and conduct trials in normal times which are capable of pivoting in response to outbreaks. Prepositioning work by clinical trial networks should include pathogen agnostic trial protocols for multiple physiological systems that could be affected by an outbreak pathogen, building on existing protocols and including e.g. the respiratory, enteric, neurological and reproductive systems. In this way networks and protocols can answer the most compelling clinical research questions in normal times in endemic diseases, and iteratively improve capacities to be available at the time of emergencies. Such protocols should be capable of implementation rapidly in future emergencies.

Trial preparedness by networks should include all the elements needed, including personnel, processes for ethics approvals, contracts and financial envelopes for emergencies, ready to be activated. Several respondents noted that it is not possible to develop new research contracts quickly during emergencies, thus placing a focus on pre-establishing contractual mechanisms such as with standing network contracts that have a budget envelope available which can be triggered for disbursement during emergencies. Contracts in place should include the expected time to trial implementation. For example, preparedness work by networks should enable clinical descriptive studies to begin within very short periods, and trials within a few weeks.

Development of platforms for clinical trials should occur in the inter-pandemic phases in such a way that they can be activated when a crisis happens. REMAP-CAP was highlighted as a good example. When the pandemic emerged, enrolment began very quickly. In between pandemics, the platform could be used to evaluate treatments for viral infections, such as influenza and respiratory syncytial virus. This was highlighted as an example of structures built that provide added value in normal times, with design features that allow for rapid utility in emergencies. Such platforms for enrolment in primary care remain a key need and gap.

4) Perspectives on prioritization and coordination

Collaboration and coordination between researchers is central to optimizing health outcomes from trials. Several respondents indicated that greater collaboration is needed throughout the clinical development pathway to align on assays, outcomes, endpoints, standards and protocols so that robust data can be generated in comparable ways. There are many steps stakeholders in the clinical trials ecosystem can take to improve collaboration and where possible, develop standardized outcome measures that are relevant to populations that the intervention is intended to benefit, regulators and policymakers.

Most respondents indicated that they consider WHO's primary role in clinical trials is to act as convenor, to assess evidence and provide evidence-based recommendations including for WHO Guidelines and Prequalification. Some respondents pointed to what they saw as an important role for WHO in developing global priorities for publicly funded research through an inclusive convening process, as was done by the WHO R&D Blueprint during the pandemic. Public funders should coordinate their efforts (via fora such as GloPID-R), link their funding to a well-coordinated research agenda, which may be developed through a WHO convening process, and share information about research that they are funding clearly and regularly to help WHO and others to have sight of key research funding needs and gaps. Clinical trial networks addressing both epidemic and endemic diseases regionally and internationally should also co-ordinate their activities.

Large publicly funded trials, especially during crises, need to be supported at a national (political) level. Such high-level prioritization of clinical trials can ensure transmission through the whole chain of decision makers and encourage optimization of trial quality, size, speed, conduct and sustainability. Excellent academics, ideas and proactive protocol development are not sufficient without long-term investment in trial and research networks at national and regional levels, including coordination mechanisms.

Many respondents indicated that national research priorities and coordination mechanisms were seen to function effectively in the UK during the Covid-19 pandemic, where a coordinated mobilization of infrastructure, including in primary care, led to massive recruitment in a number of publicly funded platform trials. The successful research response in the UK was enabled by the National Institute for Health and Care Research (NIHR) and its Clinical Research Network, which is an example of how practical research can be embedded at high quality within a health system. Mechanisms for dialogue and coordination are needed to ensure alignment in the selection of research questions, leading to more rapid site initiations, inclusion of participants and generation of evidence. Coordination can help to reduce the number of small unimpactful studies and ensure that the most adequate study designs are used to assess the most relevant interventions and settings. It was noted that a series of actions are needed by funders, healthcare providers and approval bodies to prevent poorly designed small scale uninformative trials – many thousands of which occurred during the COVID-19 pandemic. One funder reported that they consider post-funding scientific design reviews of trial protocols and statistical analysis plans as a best practice. According to the funder these reviews should focus on ensuring that trials are optimized for an informative outcome.

Governance and coordination mechanisms need to be established in normal times, with provisions for how they will function in the case of emergencies. There are a number of strategically important topics that would benefit

from coordination. These include how best to ensure high quality, policy relevant clinical trials. A common understanding has not necessarily been reached on how best to implement a good quality trial at international level. Critical questions raised by inputs included; should all clinical trials have dedicated methodologists? To what extent and how is the Data Safety Monitoring Board (DSMB) consulted during the trial? How best can recruitment occur (and trials be tailored) for distinct vulnerable populations? Some respondents indicated that there is currently insufficient integration of methodologists and statisticians in trials. In the coordination, funding and governance of trials, how can programmes best be tailored to produce high quality results rather than to promote individual academic careers? In the area of clinical trials, it was stated that the academic reward system should seek to reflect a common research goal rather than incentivize individual academic merit.

5) The role of adaptive platform trials

A key learning from the pandemic is that there is insufficient time to set up a new trial with every new potential treatment, hence the need for dynamic platform trials and pragmatic evaluation focusing on trial data collection and procedures that are applicable to a range of treatments. In order to implement adaptive platform trials effectively the prioritization and coordination elements designed above are needed, as are trial protocols that are suitable for implementation internationally with a focus on the key scientific and ethical elements needed for participant protection, and valid interpretation. It is a common perception that the acknowledgement of the importance of primary care trials came too late during the Covid-19 crisis. Knowledge of how to prevent people from getting admitted to hospitals was essential to prevent a collapse of the health system and could only be obtained through large-scale trials of early treatments that are designed and delivered to the community at large scale through adaptive platform trials. In primary care, there is also a need for better ways to attract patients to research. WHO's health ethics unit will publish a series of articles during 2023 on the implications of adaptive platform trials for ethical approval processes. Platform trials also highlight more general problems with lack of efficiency in oversight of very large multi-site and multi-country trials. Procedures are needed to rationalize the numbers of approvals required, reduce time to approval and ensure coordination, harmonization and streamlining of what can be over 50 sets of approvals.

In general, adaptive platform trials have been publicly funded, have included multiple interventions concurrently, have used prioritization procedures to decide which interventions to include, and have played a major role in generating evidence for WHO guidelines and other recommendation processes.

Some inputs linked collaboration and incentive structures to the chances of success of platform trials going forwards. For this model to be successful, those participating will need to consider their participation a success with appropriate incentives and rewards. If incentives are to collaborate towards shared goals, these could align well with an expansion of collaboratively designed platform trials; if academic incentives remain linked to personal recognition and first author publication the incentive for small and potentially uninformative trials continues.

6) Specific considerations for clinical trials in resource limited settings

Many respondents noted the availability of the recent CIOMS guidance "Clinical research in resource limited settings" which is considered an extensive and useful guidance with concrete suggestions for various stakeholders to advance clinical research in resource limited settings. Many of the other sections of this report contain paragraphs which focus on LMIC where both the biggest gaps in capacity and infrastructure exist, and the greatest needs for clinical research are found due to the high burden of disease.

Here we focus on one area where specific inputs were received, considering the equal representation of LMIC stakeholders. Respondents appreciated that large, international trials are sometimes required in order to ensure that populations that are most in need of interventions are included, so that results can be best extrapolated to

areas of greatest disease burden. It was also noted that this is a shifting landscape, with for example public-private partnership models as well as greater private and public sector capacity for research created in the last 2 decades in some LMIC, that have contributed to the development of new medical products. However, it is important to stress that it is essential to include LMIC representation in all aspects of the prioritization, protocol development, trial implementation and reporting cycle. The research prioritization process should include LMIC stakeholders, including those from the population intended to benefit, as well as policy and regulatory representatives. Any country or region will have a greater interest in a project if it pertains to a major public health problem relevant to their population. Directing international funding resources towards unmet and neglected needs of underserved and developing country populations may need extra effort and careful planning.

One area where more work is needed is to ensure that trials conducted in low and middle income settings are indeed aligned with the local priorities of patients, communities and policymakers, to ensure results are always communicated appropriately to these stakeholders, and then to develop good mechanisms to implement high quality findings into local practice. It has sometimes been the case in the past that international trials support the needs of sponsors in other countries, and that interventions that are licensed based on cases accrued in high burden settings, are not always available in those high burden settings. Respondents indicated that this is ethically not acceptable and should be avoided. The CIOMS guidance goes into detailed discussion on this topic. IFPMA has welcomed the CIOMS report, and published its perspectives on it.

7) Gaps in data on specific population groups and disease targets, and gender biases in data

Inclusive participation is essential for clinical trials to support decision-making in all populations in need. Respondents noted that there are a number of specific gaps in evidence generation from clinical trials which may result in these groups being precluded from access to needed interventions. Such gaps include, but are not restricted to, paediatric data and data from pregnant and breastfeeding women, as well as gaps in sex, racial and ethnic representation in clinical trials. Best practices to address the historical male bias in clinical research that some respondents highlighted, may include prioritizing the integration of sex-gender considerations into clinical trial planning and execution; including disaggregation of study data by sex; include sex-gender dimensions in the condition(s) being studied; eligibility criteria supporting representative sampling and sensitive to gender aspects of recruitment, retention and adherence. There are current weaknesses in the evidence base including 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.

There are some specific initiatives that seek to address some aspects of these gaps, but additional resources and considerations are needed to improve the current status quo. For example 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 may contribute to operationalizing resolution WHA75.8 by streamlining the generation of clinical evidence and promoting best practices for paediatric medicines research and development. It was highlighted that for initial trials there may be a justification for excluding some groups from enrolment for safety reasons. However, there is also a need to include key groups to ensure such populations can safely use the products developed in trials, and to confirm effectiveness in these groups. Further work is needed as a priority to accelerate the responsible inclusion of these populations appropriately in clinical trials. Some respondents highlighted that generation of data on safety and effectiveness of medical products in pregnant women remains a neglected area, although the RECOVERY trial was noted to be an example of success in enrolling pregnant women. Some respondents noted there could be requirements to justify exclusion of pregnant women for trials of therapeutics and preventives, and to outline additional studies planned to evaluate safety and effectiveness in pregnant women beyond animal toxicity studies. It was suggested that putting women's voices at the heart of

the relevant regulatory authorities is central to maintaining public trust and ensuring that such actions are enabled.

For international trials, local researchers are best placed to determine the best modalities to encourage diversity of enrolment in clinical trials in locally appropriate ways. Patient and public engagement are particularly important for the process of including underrepresented populations in clinical trials. Respondents highlighted that trial registries, and dedicated resources or initiatives to support enrollment of under-represented populations, have been successful in some contexts. Implementation research may have a role alongside clinical trials to develop successful methods to increase participation of historically underrepresented groups. Several respondents highlighted the importance of collecting post-marketing data from those receiving interventions. These can sometimes be the only available data on safety and effectiveness in certain populations.

Conclusion

The inputs summarized above, with full inputs made public where permission has been obtained, serve as important parts of the consultation process as WHO moves forward with the guidance requested by WHA 75.8.

The secretariat provides this longer report in time to be available for deliberations at EB 152, and will take them into account, as appropriate, as part of standard WHO processes, in developing new guidance as needed.

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