Clinical Trials in Global Health 6

A roadmap for fostering timely regulatory and ethics approvals of international clinical trials in support of global health research systems

Marco Cavaleri, Claudiosvam M Alves de Sousa, Adam Hacker, Elisabeth S Higgs, Murray M Lumpkin, Christiane S Maia, Roli Mathur, Adam M Fimbo, Andreas Reis, Kyoung Seung Shin, David W Vaughn, Wei Zhang, Vasee Moorthy

The global clinical research ecosystem faced highs and lows during the COVID-19 pandemic. Key issues included research waste from poor-quality trials and fragmented regulatory and ethical reviews. Streamlining and harmonising these review processes is crucial for efficient, robust, and timely multinational trials, ensuring rigorous scientific standards, proper safety, and ethical oversight. Robust regulatory and ethics review systems thrive on continuous learning and efficient processes, crucial for high-quality research. Enhancing trial design and implementation, and guiding innovative approaches including decentralised trials and patient-centric designs are essential for the regulatory and ethics authorities to advance public health. These approaches are built on the principles of global guidance outlined in International Coalition for Harmonization Good Clinical Practice guidelines and the WHO guidance for best practice for clinical trials. To realise the agreed vision at the first WHO Global Clinical Trials Forum in 2023, a panel of international experts in clinical research, including representatives from national and regional regulatory and ethics authorities, proposes key actions to improve coordination and streamlining of regulatory and ethics review. The actions emphasise: leveraging existing trial networks and capacity-building initiatives; advancing joint and parallel regulatory and ethics reviews and single national ethics review; improving transparency on approval requirements; simplifying and standardising informed consent forms and processes; and developing mechanisms to improve efficiency for trial site contracting as well as exportation and importation of investigational products for trials. The proposed actions for the reform are urgent and key to generate evidence to enable access to safe and effective interventions for populations most in need.

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Public Health Threats Department, Emergency Task Force, European Medicines Agency, Amsterdam, Netherlands (M Cavaleri PhD); **Coordenação de Pesquisa Clínica em Medicamentos e Produtos Biológicos (Copec) Agência Nacional de Vigilância Sanitária - Anvisa, Brazilian Health Regulation Agency, SIA, Brazil** (C M Alves de Sousa MsC, C S Maia PhD); **Coalition for Epidemic Preparedness Innovations, Oslo, Norway** (A Hacker PhD); **Division of Clinical Research, National Institute of Allergy and Infectious Diseases, US National Institutes of Health, Bethesda, MD, USA** (E S Higgs MD); **Integrated Development, Bill & Melinda Gates Foundation, Seattle, WA, USA** (M M Lumpkin MD); **Bioethics Unit, Indian Council of Medical Research, Bangalore, India** (R Mathur PhD); **Tanzania Medicines and Medical Devices Authority, Ubungo External, Dar es Salaam, Tanzania** (A M Fimbo PhD); **Research for Health Department, WHO, Geneva, Switzerland** (A Reis MD, W Zhang PhD, V Moorthy PhD); **Clinical Trials Policy Division, Ministry of Food and Drug Safety, 187 Osongsaengmyeong2(i)-ro, Osong-eup, Cheonju-si, South Korea** (K S Shin MS); **Clinical Trials Policy Division Bill & Melinda Gates Foundation, Seattle, WA, USA** (D W Vaughn MD)

Introduction

The overall landscape of clinical trials is affected by both the quality of clinical trials submitted for approval and the ability of competent authorities to provide timely and scientifically compelling decisions. The global clinical research ecosystem faced highs and lows during the COVID-19 pandemic. Despite some important achievements, there was considerable research waste where poor-quality clinical trials were approved or allowed to proceed without adequate power and scientific rigour to achieve actionable reliable results. A second area of waste was slow, inefficient, sequential, and fragmented regulatory and ethical reviews negating efficient accelerated global conduct of robust clinical trials.[1–3] It is crucial to consider actions for streamlining and harmonising ethical and regulatory clinical trial review processes. Long-standing inefficiencies in clinical research stem from the absence of a harmonised, universal approach to the review, approval, and initiation of international clinical trials. The vision is to develop efficient, global, streamlined, and consistent processes to enable the timely launch of informative, multiregional trials upholding rigorous scientific standards and proper safety and ethical oversight.

Multiregional clinical trials have the advantage of ensuring large groups of investigators from different geographies can be involved, which helps reach the required sample size in a short timeframe and better compensate any regional or local variation in the number of participants that could be eligible. These types of clinical trials maximise the generalisability of the results across countries and regions which further strengthens the robustness of conclusions.

Regulatory authorities as well as research ethics committees and institutional review boards (RECs and IRBs) are the entities responsible for approving clinical trials initiation and providing oversight, irrespective of the substantial variation in roles and responsibilities of these bodies across countries and jurisdictions. For specific definitions and roles of all the different players please refer to International Coalition for Harmonization (ICH) documents.[4,5] Review of multinational clinical trials across a diverse range of diseases shows that sequential submission to ethics committees and regulatory agencies within and across countries results in unwarranted delays in obtaining final approval to enrol participants. This fragmentation of regulatory and ethics reviews impedes efficient initiation of large multinational clinical trials, which once rectified, could swiftly yield consolidated evidence on the potential benefits and risks of interventions.

Reviews of lessons learnt with respect to options for improving timely start of clinical trials have been conducted by some regulatory bodies, including by the

Correspondence to:
Dr Marco Cavaleri, Public Health Threats Department, Emergency Task Force, European Medicines Agency, Amsterdam 1083 HS, Netherlands
marco.cavaleri@ema.europa.eu

European Medicines Agency (EMA).[6–8] The African Vaccine Regulatory Forum (AVAREF) utilises a joint regulatory and ethical review process, which has led to, for example, phase 3 clinical trial approvals for malaria vaccines—products that have now successfully achieved WHO prequalification, local marketing authorisation, and policy recommendation. The AVAREF joint review has both standard and accelerated timelines depending on the situation (ie, from 60 days to 30 days or even 15 days in case of emergency). More recently, AVAREF has been able to offer clinical trial sponsors of multinational clinical trials joint scientific advice on clinical trial design and process issues.[9]

The absence of a cohesive global regulatory and ethical review framework, including alignment on trial requirements and timelines, hampers the development of sustainable clinical research systems capable of swift responses to health emergencies. This state leaves the world vulnerable to future epidemics and pandemics. WHO convened the first annual Global Clinical Trials Forum in November, 2023, to facilitate discussions on continuous global clinical trial infrastructure. The vision is: always on and always ready. As part of this endeavour, WHO convened a regulatory and ethics working group to facilitate a multistakeholder dialogue on tangible improvements towards transparent, rigorous, and timely trial authorisations.[10] This paper summarises suggested areas of actions that will improve needed efficiencies in ethical and regulatory reviews.

Points to consider

A robust regulatory and ethics review system thrives on continuous learning from reviewing clinical trial applications. The volume and calibre of clinical research in different regions substantially influence the efficiency and rigor of regulatory and ethics reviews. Regions with opaque or lengthy approval processes might deter researchers and sponsors, perpetuating a cycle of poor experience and proficiency. Breaking this cycle requires building and maintaining functional clinical trial infrastructure that encourages dialogue with regulatory and ethics authorities. This approach fosters sustainable capacity for efficient, high-quality research, benefiting both public health and economic outcomes. Enhanced efficiencies will streamline global studies and promote equity in developing local and regional clinical trial capacities, broadening options for sponsors in selecting countries and clinical sites.

Global standards in ICH guidelines, E6(R3) on good clinical practices and E8(R1) with general consideration on clinical trials, and WHO guidance for clinical trials, aim to harmonise trial design, execution, and ethical oversight. Although the scope of ICH E6(R3) is for clinical trials of investigational products for submission to regulatory authorities, the scope of WHO guidance is much broader, applicable to any clinical trial, with any design. These guidance documents support efficient regulatory and ethical review across sites, countries, and regions, and are aligned on the key importance of proportionality and risk-based approaches, prioritising participants' safety and trial result integrity.[4,5,11] These guidelines encourage a fit-for-purpose approach that recognises that trial design, implementation, and oversight might vary depending on the trial's purpose, existing knowledge of the interventions, and the population to be enrolled. For example, a pivotal confirmatory trial for a new agent, which confirms the clinical hypothesis to support the demonstration of efficacy, differs substantially from a pragmatic trial, which provides evidence on the intervention in real-world clinical practice, with a repurposed agent or as post-approval evidence generation for an approved product.[4,5,12]

Clinical research must prioritise ethical integration to advance public health through universally beneficial knowledge. Ethical evaluation is more than review; it is about stakeholders upholding shared values across cultures. This approach includes ensuring scientific validity and the local societal value for participants, respecting autonomy through informed consent, inclusive participant selection, improved community engagement, thorough benefit-risk analyses, and ensuring participant safety and wellbeing. Research institutions have an important role to play in fostering a culture of ethical conduct by providing ethics training to their researchers, enabling an efficient ethics review, developing patient-centric informed consent forms that are concise and clear, and ensuring that researchers are meeting their obligation to protect participants' rights, safety, and welfare.

A healthy research ecosystem views the ethical dimensions of research as constitutive to research excellence.[13] Investigators have a leading role in ensuring that the proposed clinical trials address relevant research questions and that the design of the study can provide meaningful results. Prioritisation, especially, but not limited to, emergency settings, needs to be constantly considered together with opportunities for collaboration with larger endeavours for clinical trials focusing on the same research areas to avoid fragmentation and duplication. To what extent authorities (eg, regulators) should act as gatekeepers in selecting what clinical trials have the potential to produce meaningful results needs to be further discussed. However, there is a clear need to consider how regulators could steer clinical research towards minimising the research waste in the best interest of patients.

Regulatory and ethics communities need to remain updated and informed to actively support innovations, new tools, and approaches to increase trial efficiency by streamlining their conduct. For example, decentralised clinical trials are modalities aiming at increasing efficiency and reducing the burden to participants and investigators.[14] Patient-centric clinical trials are an area of growing interest and would represent an opportunity for

introducing innovative approaches to trial design and conduct.[15]

Proposed actions

Supporting sustainable clinical trial networks and capacity building

To achieve a truly global capacity to conduct equitable, robust, and timely clinical research, capacity building is necessary to support regulatory systems in low-income and middle-income countries (LMICs). Ideally each country will reach a maturity level three on the WHO Global Benchmarking Tool for clinical trials oversight to ensure proper review.[16] Sponsors should be encouraged to conduct clinical trials in those countries with clinical trial networks that include a focus on enhancing sustainable clinical trial infrastructure meeting local and national needs. Such occurrence will also provide learning and experience to the ethics and regulatory authorities. Local investigators should also play a key role in selecting priorities and making sure that clinical research addresses local needs. Once clinical trials are completed, it should be warranted that effective and safe medicinal products are made rapidly accessible and affordable in places where the clinical research was conducted.

Commitments must also be given to maintain continuous clinical trial networks to keep active sites, regulators, and ethics committees to ensure research capacities are not lost after a trial is completed and would have to be re-built in the future when the need for a new trial arises. Consideration should be given to defining common operational processes so that clinical sites do not have to learn new processes for every sponsor.

Forums should be provided for continuous engagement and learning between regulators, ethics committees, the clinical research community, and clinical trials networks to ensure shared understanding of the scientific and public health goals and facilitate agreement of sound clinical trial designs. More opportunities for such scientific engagements should be foreseen. Training and courses for investigators on research ethics, good clinical practices, and research integrity need to be systematically organised.

Advancing the single REC model per country for multicountry trials

To streamline the review process for multinational clinical trials, one REC per country would be ideal. This approach would enable faster decision making and ensure consistency in deliberations, easing collaboration with countries or jurisdictions for international trials. The implementation of this model would vary depending on the size and diversity of the country. For example, in a large and diverse country such as India with more than 4000 RECs, careful consideration is needed to operationalise such a model; considering local values and requirements should not be overlooked, but should not become a bottleneck. Countries where multiple, and often redundant, ethics reviews are completed at the local, regional, state, or national level, should be prioritised for action.

Implementing a centralised ethics review system could streamline approvals by having a designated central or state level ethics committee conduct a common review. Other participating bodies would then provide recommendations to study sites for local approvals, relying on the central review to expedite processes and avoid redundant reviews. Similarly, a regional approach within an economic community could involve a joint or selected member completing a single ethics and regulatory review for the entire community. Countries within the supranational communities (eg, the EU) could then expedite local reviews based on the regional assessment, considering local relevance without duplicating the review process.

Defined core information in the ethics committee application, such as clinical trial protocol and informed consent, could be reviewed only once. The more variable components in the application, which might require specific local adaptation, could be reviewed also by local ethics committees. Although much has been accomplished by ICH and WHO in the regulatory space to promote alignment in regulatory processes, very little has been done historically in this regard in the ethics board space. A related approach would be the mutual recognition and reliance of ethics committees' decisions by different research institutions. WHO promoting an effort to harmonise and align ethics board procedures would help build the foundation for greater acceptance of reliance-based ethics board reviews and promote transparency and predictability in the review process. In addition, no communication channels exist to facilitate ethics review; a network between the participating site ethics committees should be built to encourage robust and harmonised ethics reviews for multicentric trials.

It would be beneficial for WHO to perform a mapping of established processes and legislation in place with respect to REC in all countries. For example, mapping could be done to identify how many countries have a single central REC model, under which circumstances they operate, and to capture any relevant regulatory provisions in these countries. Such mapping is expected to help in advancing tailored actions and improving approaches to clinical research.

The benchmarking of REC capacities with the use of the WHO benchmarking tools analogous to regulatory capacity should facilitate reliance on reviews done by a trusted ethics committee, which has been certified by WHO as performing well and consistently with respect to international standards. Similar to reliance in the regulatory space, this framework does not infringe sovereignty of countries, and it does allow local considerations to be included. Trial sponsors should require, or encourage, protocol reviews by WHO

benchmarked ethics committees, which will ensure quality review, build a research environment, and ensure consistency with respect to international standards.

Stakeholders frequently emphasised the need for integrating ethical considerations throughout the entire clinical research process, from planning to post-trial stages. This approach entails raising investigators' awareness of ethical and regulatory requirements and fostering proactive communication between researchers and ethics committees through mechanisms such as pre-submission meetings. We suggest ethicists should be engaged early in the process of protocol development, which usually facilitates addressing the thorniest ethical issues even before the protocol gets submitted to an ethics review committee. Enhanced community engagement can tailor trials to local needs, whereas dialogue between sponsors, ethics reviewers, and regulators can streamline the review process. Initiatives such as AVAREF's pre-submission meetings involve both REC and regulators, promoting fast approvals and reducing formal objections and requests for clarification.

All clinical trial protocols should have an ethical considerations section. For multicentric clinical trials, use of standardised forms for ethics review across multiple research sites can align submission requirements, reduce the effort needed to complete forms separately for each site, and help ensure completeness and compliance of submissions.[17]

REC require adequate staffing, full-time support, and financial resources to fulfil their roles effectively. In many LMICs, ethics review is often done by volunteers or under-resourced committees charging prohibitive fees, hindering research progress. Countries should prioritise well equipped and funded REC to promote efficiency and financial sustainability. Consolidating into fewer but stronger committees should be recommended. Overall, REC and IRBs should encourage and support harmonised review processes and should be administratively efficient.

Move to parallel regulatory and ethics reviews for clinical trials as a norm

Figure 1 describes an example of the approval process in a single country for a clinical trial to support development of a specific drug. The process involves submission to an institutional review board, committee, and national regulatory authority. Approval processes in these institutions take at least 3 months, 2 months, and 2 months, respectively, in a sequential order. A total of 7 months is required to obtain approval to start the clinical trial. This timeframe is excessively long and options to streamline the process avoiding within-country sequential reviews are warranted.

Figure 1: **Example of process flow of protocol approval**
Estimated timeline of a paediatric clinical trial for a tuberculosis drug in a country utilising a sequential review and approval process.

Clinical trial application processes need to be efficient. Ethical and regulatory reviews, as well as clinical trial materials importation permits (currently presumptive on a positive regulatory and ethics decision), should be done in parallel. Sequential review by regulators and RECs and IRBs impedes clinical trials and offers no added value. Although such processes are sometimes embedded in national legislation, and therefore without legislative changes they could not be implemented, efforts should be made to implement solutions to avoid rigid sequential review processes and allow legislation changes if that is needed.

Increased international regulatory collaboration, coordination, and transparency, including sharing of questions and responses between regulatory authorities, ethics committees, and sponsors, will streamline and accelerate the assessment process, and strengthen regulatory as well as REC and IRB capacities.

One way to improve the efficiency of the review process especially for complex multinational clinical trials is to have joint pre-submission meetings or seek scientific advice between sponsors, regulatory authorities, and REC. To facilitate these meetings, agencies, and ethics boards should develop and implement routine practices for memorandum of understanding or confidentiality arrangements. These memorandums of understanding should also be made public. Additionally, sponsors should routinely permit sharing of all clinical trial information between regulators and ethics committees in their cover letters, especially for multinational trials where confidentiality concerns can hinder the review process. Review should be optimally tailored to the objective of the clinical research, epidemiological context, and investigations considered. Simple natural history studies with specimen collections are very different types of clinical studies than pivotal clinical trials for supporting initial authorisation of a new active substance. The process and requirements need to be customised based on these elements. Actions should be explored to reduce the administrative burden and address bottlenecks in clinical trial reviews to enhance a smooth, fast, and yet effective review process.

Improve export and import of investigational products for clinical trial use

Lengthy import and export permit procedures for investigational products awaiting regulatory approval often cause delays in clinical trial initiation. Similarly, importing diagnostic or immunoassay kits for clinical trials can be delayed due to bureaucratic hurdles, possibly jeopardising trial conduct. A mapping of import and export requirements across member states could aid in understanding global disparities and facilitate harmonisation, streamlining sponsor planning, and enhancing alignment of requirements.

Implementation of joint review for clinical trial application (CTA) between relevant National Regulatory Authorities and REC for priority multicountry trials

Figure 2 illustrates an example of constraints related to review and timely approval.[18] This example highlights the risks of possible conflicting requirements of submitting to multiple regulators simultaneously. Moreover, lengthy approval timelines can be particularly challenging for adaptive trials (ie, clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on emerging data), with rapid addition and dropping of investigational agent. Some sites could not participate at all, as the approval process could not catch up with the protocol updates. Clinical trial protocol amendments in one place create discrepancies, such as conflicting inclusion and exclusion criteria, endpoints, safety monitoring, and statistical testing, from where the trial is already approved.[6,19]

Building on the experience gained for example in the African region with AVAREF, mechanisms for concerted discussion among different regulators and ethics committees on clinical trials protocols across sites, countries, and regions could be established in the next step. This change could act as a catalyst to improve convergence and speed of assessment for international trials. Strengthening regional clinical trial application assessment such as AVAREF, including lessons learnt after each review to build expertise, and increasing transparency of timelines and their various components would drive efficiency and build trust between countries and enable greater use of reliance mechanisms when timings are tight and resources are scarce. These increased efficiencies and improved adherence to timelines will support sponsor decision making with respect to the choice of country and clinical sites and will also facilitate more inclusive clinical research.

Such forums can also allow countries to send observers even when they are not part of a specific review, with appropriate consideration of requirements related to the sharing of confidential information. This strategy will allow those countries to build expertise on regulatory strengthening. The forum can provide direct joint review of the clinical trial protocol or, in advance of submission, opportunities for scientific advice to sponsors to agree on the key elements of the study design. The process around the forum can be used to define which type of clinical trials could be eligible for

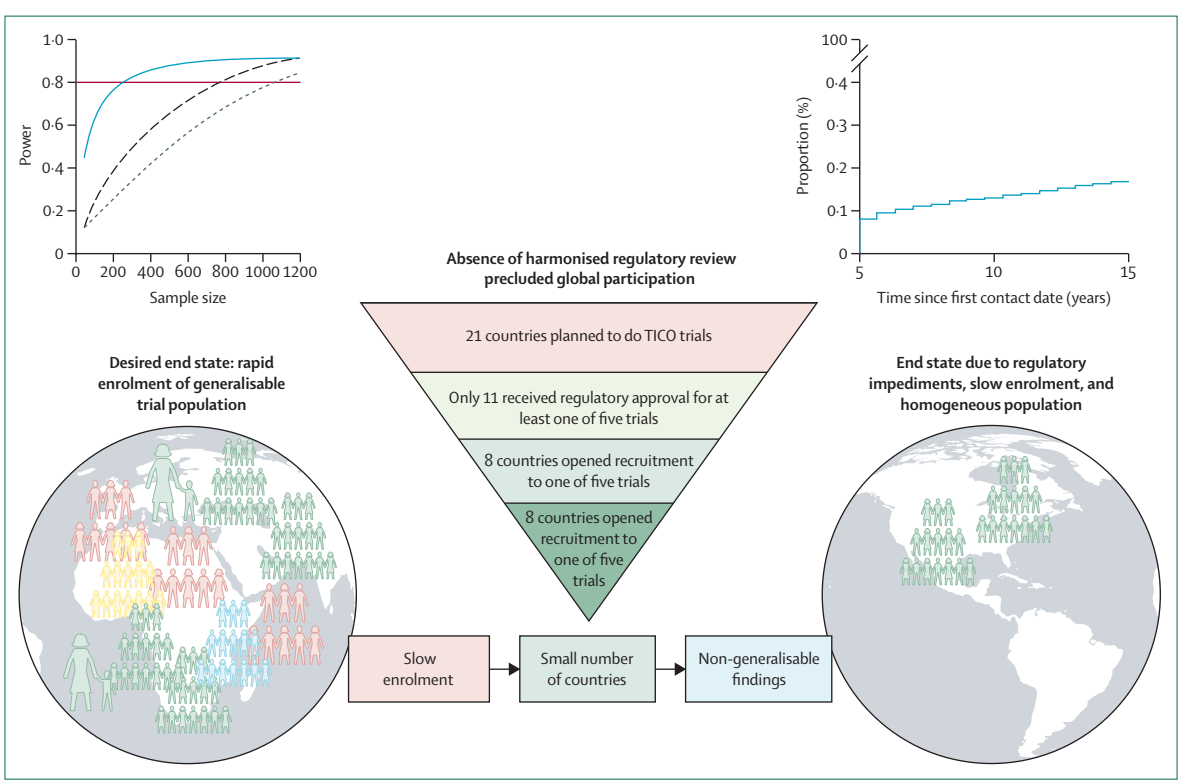

Figure 2: **Illustrates an example of constraints related to process and timely approval of a global platform trial called TICO[18]**
The example highlights the consequences of conflicting and disparate requirements when submitting to multiple global regulators. The figure shows that lengthy approval timelines can be particularly challenging for adaptive trials (ie, clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on emerging data), with rapid addition and dropping of investigational agent. In some cases, several sites and countries could not participate at all, as the approval process could not catch up with the protocol updates. Clinical trial protocol amendments in one place create discrepancies, such as conflicting inclusion and exclusion criteria, endpoints, safety monitoring, and statistical testing, from where the trial is already approved.[6,19] Without regulatory harmonisation global adaptive platform trials will struggle to be inclusive. TICO=Therapeutics for Inpatients with COVID-19.

scientific advice and joint review based on complexity, innovation, urgent unmet medical need, or any other key element.

This kind of forum should be established also for other regions. Having similar hubs of authorities in different regions, such as AVAREF or in the EU (eg, Clinical Trial Coordination Group),[7,8] would simplify the connections and interactions across regulators and ethics boards from different regions. Such broader interactions would be particularly useful when clinical trials are to be conducted in different regions, when there is a public health emergency, or when submission for marketing authorisation approval for the product is expected also in regions where the clinical trials are not planned to be conducted. In regions where these regulatory and ethics coordination forums are currently not available, they might need to be established. The need for any legislative changes to enable rapid uptake of recommendations from such new forums should be investigated, and, if needed, enacted. Otherwise, long national authorisation waiting times based on the joint review might lengthen the process despite the rapid joint assessment and recommendation.

Although regulatory and ethics committee authorisations of clinical trial application is a separate process from product marketing authorisation, clinical trials should aim to provide evidence that is actionable for regulatory decisions and public health interventions. Overall increased multilateral regulatory discussions across countries and regions to foster a shared perspective could allow rapid convergence on clinical trials design in different locations considering the requirements for products approval and recommendation for use. Increased regulatory discussions would also provide an opportunity for capacity building across regulatory bodies and ethics committees and allow these bodies with little exposure to complex clinical trials to increase their ability to efficiently conduct such reviews.

Transparency as to documents needed for Regulatory Agencies and REC approvals per country through a public database

Regulatory agencies should establish transparent timelines for review of clinical trial applications, with an additional accelerated timeline for public health emergencies. Harmonisation of required regulatory documents to simplify the process for sponsors of clinical trial applications is needed. Often there are additional documents, beyond the core documents, that are requested by authorities, which causes unnecessary administrative delays that affect clinical trial initiation.

Countries that have additional document requirements beyond ICH and WHO recommendations should clearly communicate them and re-evaluate if such documents are indeed necessary. Changes in requirements during the review or requests for additional documents that were not initially specified should be avoided, as these can slow down the approval process and discourage sponsors from conducting research in unpredictable and opaque environments.

One solution could be development of a public global database by WHO that captures regulatory and ethics requirements from all 195 member states. Each member state would be responsible for keeping their section of the database up to date. This database would identify core documents that should always be included in the clinical trial application and highlight country-specific variations. With the use of registered country-specific templates, the content of the submission could align with the country's requirements, reducing the need for ad hoc additional requests for documentation during the submission process. Availability of templates would streamline harmonised submissions but would not obviate the need for adequate explanations of the scientific rationale and ethical aspects of the proposed clinical research.

To improve the efficiency of the review process, a common CTA technical document could be developed to meet the requirements of both regulators and ethics committees. Similar to the existing marketing authorisation applications, this common CTA document would have standardised core modules accepted by all countries and a national module for country-specific information. Once these documents are identified and standardised, the next step would be to implement a single electronic submission system per country or even across countries. This system would facilitate exchanges and enable shared transparent review, leading to a more streamlined and efficient submission process.

Concerns about the disclosure of confidential information can be managed with the use of electronic tools that control access and document usage. Virtual joint reviews, as shown during the pandemic, are also efficient and effective, allowing real-time discussions and questioning in multiple languages. AVAREF successfully used this approach frequently during the pandemic.

Informed consent forms should be simplified and standardised to the extent possible

As discussed at the WHO Forum, the informed consent form (ICF) is a key document for clinical trial participants, who could benefit from a concerted effort to address the current complex, legalistic, and lengthy document that many patients deem uninformative. The ICF might impede potential participants from clearly understanding proposed research and grasp the key information on their participation in the trials. The legal aspects of the ICF are distinct from the core regulatory and ethics requirements and have a considerable effect on outlining of the ICF and increasing the complexity of the reading and understanding of the clinical research by participants.

Regulators and ethics committees are uniquely placed to promote improvements in informed consent for trial participants. A poorly crafted or communicated informed consent might reduce patients' interest in a trial, obscure

Panel: **Summary of key identified actions—specific objectives and deliverables**

Leveraging existing clinical trial networks and capacity building

- Build capacity to enhance sustainable clinical trial infrastructure following maturity level three clinical trial oversight indicators.
- Maintain always active clinical trial networks.
- Develop experience in areas of weakness within the ethics and regulatory authorities.
- Create a forum for discussion among regulators, ethicists, and research community.

Advancing the single Research Ethics Committee (REC) model per country for multicountry trials

- Map established processes, timelines, and legislation in place with respect to RECs in all countries.
- Benchmark REC capacities with the use of the WHO Ethics Committee global benchmarking tools analogous to those used for regulatory capacity.
- Define core and variable information in the ethics committee application.
- Provide central reviews by a Designated Central RECs for core information when variable portions undergo local ethics review.
- Develop approaches for mutual recognition and reliance of trusted ethics review committees' decisions.
- Ensure RECs and National Regulatory Agencies (NRAs) are sufficiently staffed, funded, and equipped.
- Eliminate dual ethics review (local and national) in countries.

Move to parallel regulatory and ethics reviews for clinical trials as a norm

- Provide joint pre-submission meetings and scientific advice between trial sponsors, ethics committes, and regulatory authorities.
- Ensure sharing of questions and responses between regulatory authorities, ethics committees, and sponsors with sponsor permission is a routine part of each application. Memorandums of Understanding and other agreements in place before applications received.
- Map the overall clinical trial approval process in countries including roles, responsibilities, fees, and timelines.
- Provide options for alleviating administrative burden.
- Institute any needed regulatory and legal changes to allow parallel review by ethics and regulatory bodies within a country.

More efficient and transparent requirements and options for both export and import of investigational products for clinical trial use

- Map import and export requirements across member states related to medicines or kits to be used in the clinical trials.
- Propose solutions for alleviating administrative burden.

Implementation of joint review for clinical trial application (CTA) between relevant NRAs and RECs for priority multi-country trials

- Strengthen regional clinical trial application assessment forums such as African Vaccine Regulatory Forum.
- Establish similar forums to African Vaccine Regulatory Forum in other regions if not available.
- Establish inter-regional forums to simplify the connections and interactions across regulators from different regions.
- Allow rapid convergence on clinical trials design in variable geographies and foster capacity building.
- Enhance learnings and capacity building (eg, by including other countries as observers in clinical trial reviews).

Transparency as to documents needed for NRA or REC approvals per country through a public database

- Develop a global database that would define regulatory and ethics requirements and timelines in all 195 WHO member states—keep it up to date by member states on an annual basis or whenever changes in their rules, regulations, or laws occur.
- Ensure transparency of database content including to developers.
- Identify core documents that should always be part of the clinical trial application and highlight country variable parts.
- Develop a common CTA technical document (analogous to the common technical document for marketing authorisations) with a core national module.
- In a second step, consider moving to a single electronic submissions system per country or even across countries for the core part and enable parallel and transparent reviews by multiple regulators and ethics committees.

Informed consent forms and process should be simplified and standardised to the extent possible

- Define and develop models for patient-centric informed consent.
- Update templates.
- Make a distinction between core content and more variable content.
- Raise example of simplification to foster streamlined approach and better subject comprehension.

Develop master agreements for clinical trial site contracting

- Prevent regulators and RECs from requiring a contract to be submitted as part of the CTA review process by either regulators or ethics boards.
- Support clinical trial networks in moving towards harmonised templates for site contracts.

information most relevant to potential participants, and affect enrolment of diverse populations. A coordinated effort to define what a patient-centric ICF and process entail, including examples of streamlined, approachable consent forms that are culturally appropriate and tailored to the trial complexity and risk, could be of substantial benefit to the broader clinical research community. Proposals should be made to update templates or reiterate the key elements that should be part of the ICF, making a distinction between core content (eg, covering the disease and key elements of the protocol) and more variable content (eg, related to community engagement). Examples of simplifications of the ICF, could be raised to foster a more streamlined approach focused on patient understanding and less on perceived liability protection.

Develop master agreements for clinical trial site contracting

Signing contracts between sponsor and clinical trial site has been identified as a rate-limiting step for clinical trial timelines and that often occurs after the regulatory and ethics approval.[7] Although it is challenging to consider what can be accomplished from a global perspective, specific initiatives to attempt to define master contract documents that are pre-agreed in most aspects ahead of time, would still be warranted. These documents are not within the regulatory or ethics remit but are sometimes asked for by authorities as part of the submission package. Demanding that a contract is submitted as a required document for regulatory and ethics approval is considered disputable. Given that the contract is key to start the trial, regulatory and ethics requests for the signed contract will further delay their approvals and hence the start of the trial. Instead, submitting the signed contract before enrolling the first patient would speed up the initiation of clinical trials considerably.

Conclusions

This paper explores high-level areas of consensus for reforms and proposes concrete suggestions for progress in each of these areas of needed reform (panel). Regulators, ethics bodies, and other national authorities might choose to review the processes in their countries to assess how best to advance reforms in these areas. WHO will continue to convene partners to enable and facilitate such reforms and drive increased transparency as quickly as possible. A sense of urgency in improving clinical trial framework is key as the status quo is restricting the efficient and robust generation of evidence and precluding or delaying access to safe and effective interventions for populations most in need.

Contributors

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