

Considerations for Regulatory Oversight of Clinical Trials in the COVID-19 Pandemic

Introduction

This document provides national regulatory authorities (NRAs) with guidance for the regulation of clinical trials (CTs) in order to promote the investigation and use of safe and efficacious medicines and other health technologies that meet health needs during the COVID-19 pandemic.¹ Well-conducted, blinded randomized controlled trials (RCTs) are considered the gold standard of clinical research and constitute the backbone of the procedure for the authorization of new drugs by drug regulatory agencies (1-3). CT regulation is focused on protecting the safety, wellbeing and rights of human subjects, ensuring trials are adequately designed to meet sound scientific objectives, and preventing fraud and falsification of data (4). During the COVID-19 pandemic, there is a moral urgency to conduct CTs that are not only ethically and scientifically rigorous, but that are also done expeditiously.

The authorization and control of clinical trials considers ethical and scientific aspects that, according to the governance model defined by each country, assigns roles and responsibilities to various institutions, the most relevant being NRAs, research ethics committees, and, perhaps, other agencies such as the Ministry of Health and/or those with science and technology remits. These institutions must articulate and develop the requirements, guidelines, procedures and forms necessary to align with national, regional, and international guidelines, reflecting the principles enshrined in the Declaration of Helsinki (5), the International Ethical Guidelines for Health-related Research Involving Humans of the Council of International Organizations of Medical Sciences (CIOMS) (6), The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (7), those of good clinical practices of the World Health Organization (WHO), and Pan American Health Organization (PAHO) guidance for ethics review and oversight during a pandemic.

Pandemic situations are particularly challenging for NRAs with regards to CTs because of the proliferation of similar trials focused on analyzing the same hypotheses and medications, many of which, because of their design and execution, are not capable of delivering robust results (8). This causes competition for the recruitment of patients and eliminates the opportunity to test other hypotheses. Furthermore, the lack of coordination between multiple trials limits the opportunity to carry out direct and cross comparisons with other treatment options. Thus, multicenter, multinational clinical trials are preferable designs in pandemic scenarios. These can evaluate multiple interventions in a coordinated manner, complete faster the number of participants needed to reach conclusions when pooled together, and allow adaptation to the country. Such adaptive designs (9) allow for the worst-performing interventions to be quickly discarded and promising new treatment options to be quickly added. In addition, these trials share commonly agreed upon and defined endpoints, inclusion and exclusion criteria, a common statistical analysis plan and allow for cross-country comparisons if adequate numbers of participants are enrolled in each participating country. There are also challenges

¹ WHO defines different phases of a pandemic for influenza, including: the alert phase; pandemic phase; transition phase; and interpandemic phase. The alert phase is when a new strain of influenza is identified in humans. The pandemic phase is the period of global spread of the new strain. The transition phase is the de-escalation of global actions to address the pandemic. The interpandemic phase is the period between pandemics.

to multicenter trials, including the need to obtain approvals in each institution/country, different regulatory contexts, the coordination of multiple personnel, etc. If not multicenter, a good practice has been to use standardized protocols for trials in different locations (10).

Using WHO criteria and other relevant international frameworks, this document: 1) indicates the regulatory capacity necessary to effectively oversee CTs in general, 2) clarifies the adjustments that are needed to ensure adequate oversight of COVID-19 CTs, and 3) provides general guidance for the oversight of CTs unrelated to COVID-19 and the emergency use of unproven interventions outside of CT and research contexts. It does not discuss other types of research beyond CTs (e.g., observational studies).

Key indicators for regulatory oversight capacity of CTs

According to WHO, the regulation of CTs is a key function of NRAs (4). However, it is one of the functions that has limited levels of implementation across the Americas.² WHO’s regulatory system evaluation tool, the Global Benchmarking Tool (GBT), provides indicators to assess this function (4). NRAs are responsible for the regulation of CTs at different stages: 1) when they are being proposed for approval, 2) when they are being monitored, and 3) when they are part of the results submitted for marketing or use authorization, including under emergency circumstances.

Countries must ensure they have the necessary capacities for oversight if CTs are occurring in their jurisdiction. Table 1 includes a summary of recommended indicators for CT regulation in a pandemic based on PAHO’s knowledge and experience. These include all WHO “maturity level” (ML) 1 and 2 indicators (the most foundational), plus important ML 3 indicators. Relevant cross-cutting indicators, though important, are not included in the table, including those that promote transparency, accountability, and communication, such as funding of the research ethics committee (REC) and its membership, and the performance and output of the regulatory system’s oversight of CT. For background and the complete list of indicators, please see the clinical trials module in the GBT tool (11).

Table 1: Recommended Legal Provisions, Regulations, and Guidelines Indicators for CTs

Indicator	Maturity Level
Require legal provisions and regulations for CT oversight.	1
Permit regulatory systems to recognize and use relevant CT decisions, reports or information from other NRAs or from regional and international bodies.	1
Explain how CT oversight will function in exceptional circumstances such as pandemic emergencies. These should provide clear directives on the conditions that trigger these situations, the content of CT applications, and the scope of the review.	2
Require a structure with clear responsibilities to conduct CT oversight	2
Require guidelines for format and content of CT applications	2
Require monitoring and reporting adverse events to the NRA (AEs) during a CT. There must be guidance on monitoring and follow up if AEs are observed, clear definitions of the responsibilities	2

² According to PAHO National Regulatory Authority assessment data, 11/35 (31%) of countries in the Americas have no CT legal provisions. These are countries with limited legal basis and organizational structures for regulatory systems, which tend to be countries with smaller populations.

of stakeholders involved, and instructions on the type, nature, and form of adverse reactions to report and the timeframes for such reporting.	
Require relevant stakeholders (including research centers, researchers, sponsors, clinical research organizations (CROs)) to comply with Good Clinical Practices (GCP). GCP is an international ethical and scientific quality standard that helps ensure human subjects’ rights and safety are protected and that the data from the trial are genuine and auditable.	2
Require the establishment of a REC. CT protocols must be reviewed and approved by the REC. Note that there can be RECs at different levels of the country.	2
Require the notification and authorization by the NRA of any changes or variations in the original protocol or in relevant documents of the CT.	2
Permit the regulatory system to inspect, suspend, or stop CTs. GCP inspection of CT sites is an important oversight tool.	3
Require NRA authorization for import or destruction of investigational medical products and that they comply with good manufacturing practices (GMPs). GMPs help ensure that products are consistently produced and controlled according to quality standards.	2, 3 respectively

Furthermore, for an adequate oversight all CTs must be prospectively registered in a public registry that is part of WHO’s International Clinical Trials Registry Platform (ICTRP: <https://www.who.int/ictrp/network/en/>). The following registries in the Region of the Americas are part of ICTRP: Brazilian Clinical Trials Registry (ReBec), Cuban Public Registry of Clinical Trials (RPCEC), Peruvian Clinical Trial Registry (REPEC) and ClinicalTrials.gov. In the context of the pandemic this registration of CTs is essential: It is the only way to know which CTs are already being conducted, along with the basic characteristics of those CTs. Registration in one of these CT registries must be done in addition to any local requirement to register CTs in national registries that do not feed into ICTRP and are thus not identifiable when one conducts a global search (12).

Adjustments to ethical and regulatory oversight of CTs during the COVID-19 pandemic

Conducting CTs during the COVID-19 pandemic can be challenging but must not compromise ethical and regulatory oversight (13). The pressure to accelerate research and the need to conduct rigorous studies in emergency contexts must be balanced in order to streamline the production of knowledge on the safety and efficacy of COVID-19 preventive and therapeutic interventions. Furthermore, the pressure to accelerate CTs should not come at the expense of conducting preliminary research to determine which interventions are adequately justified to be tested in a CT, assessing ongoing CTs that may be producing relevant evidence within a short timeframe, and evaluating which CTs should be prioritized in scenarios with limited resources to conduct rigorous CTs.

To respond to the COVID-19 pandemic, RECs, health authorities and NRAs must depart from the way they usually conduct their work and develop procedures that adjust to the context of the pandemic and are able to catalyze rigorous CTs.

Some important recommendations to adjust ethical and regulatory processes during the pandemic are the following:

1. Avoid duplication of efforts, both within a country and between countries.
2. Ensure flexibility in the processes to focus on the essential issues, avoid unnecessary delays and avoid practical obstacles (e.g., conduct simultaneous reviews of CTs between RECs and NRAs).

3. Establish efficient and safe channels of communication (i.e. through electronic means) to advance coordination between and within (where appropriate) RECs, health authorities, NRAs and investigators.
4. Set tighter deadlines for ethical and regulatory processes.
5. Prioritize existing resources for the oversight of COVID-19 CTs.

Ethics review and oversight

Ethics approval via an REC must be obtained for all COVID-19 CTs before they begin. Ethical oversight of CTs must be strengthened because the large volume of COVID-19-related studies being conducted leads to rapidly changing evidence, which may imply that interventions initially considered ethical may no longer be ethical with new evidence. However, standard ethics review and oversight processes will delay the initiation and hamper the follow-up of CTs during the emergency. Mechanisms to adapt existing ethics review and oversight procedures must thus be implemented.

As described in PAHO's *Guidance and strategies to streamline ethics review and oversight of COVID-19 related research (14)*, ethics review of COVID-19 CTs during the pandemic must adhere to the recommendations listed above. As a first step, health authorities (and RECs, if appropriate) are advised to assess and choose a strategy to avoid duplication and delays. Strategies include the creation or designation of one REC that assumes responsibility for all COVID-19-related CTs. This could be done as an ad hoc committee, or at the national, sub-regional, provincial/sub-national, or institutional levels depending on the context. It is highly recommended that each country has one REC that is responsible for COVID-19 CTs within its jurisdiction. RECs can divide responsibilities based on the type of CTs, e.g. one REC could be responsible for all CTs of therapeutics while another one is responsible for all vaccine CTs. If more than one REC will review the same COVID-19-related CT, mechanisms to coordinate and communicate effectively must be implemented. In this scenario, it is recommended that RECs agree on a single REC whose review and decision will be binding for the other involved RECs.

Notwithstanding the strategy adopted in the jurisdiction during the pandemic, every REC reviewing COVID-19-related CTs must adapt their standard operating procedures (SOPs) to conduct rigorous ethics review and oversight while avoiding unnecessary delays. Strategies to do this include:

- *Digital communications and document submission.*
- *Flexibility in the requirements for document submission* - RECs should not necessarily reject studies due to, for example, missing documentation, but can instead require researchers to respond to gaps in information within a reasonable time frame. RECs should consider waiving, reducing or delaying the payment of fees for COVID-19 CTs.
- *Virtual meetings.*
- *Staggered review and decision-making* - Members may not be able to carry out virtual meetings. It may be thus appropriate to conduct the entire review process (including the deliberation leading to the REC's decision) in a staggered manner.
- *Reduced quorum* - A lower than normal quorum may be allowed and members can send in comments, questions, and reviews electronically to be counted for quorum.
- *Tight deadlines* - It is necessary to set tight timelines for the review of protocols, meetings, communications with researchers, time to receive responses from researchers, and final decisions. The REC should review the research protocol within 72 hours of receipt, and the researchers should respond within 48 hours.
- *Minutes and digital archive of REC documentation.*

It should be highlighted that these modified procedures do not imply a departure from the ethical standards to which CTs must adhere in emergency and non-emergency situations. For example, while participants in CTs during the pandemic must provide ethically valid informed consent as specified by the CIOMS Guidelines, it is necessary to depart from usual processes to minimize risks for health care professionals, investigators and research participants. Accordingly, novel mechanisms to register the expression of consent, such as digital forms or audiovisual means, must be considered.

Detailed guidance for RECs to develop or adapt their processes in the current pandemic can be found in PAHO’s *Template and operational guidance for the ethics review and oversight of COVID-19-related research* (15). This document includes specific templates for the preparation of the REC that will be reviewing COVID-19 CTs (e.g. composition of the REC, selection of members and independent consultants, etc.); the ethics review process (including documents needed to initiate the review); and ethics oversight (including how to conduct followup and monitoring).

Regulatory oversight

The changes recommended in the NRAs approach to CT regulation during a pandemic are discussed below according to the major stages of oversight.

CT Approval

Regulatory oversight of CTs must proceed more expeditiously during an emergency (4,15). Various actors may initiate requests to the NRA for CT approval. A sponsor may wish to conduct a CT in the country, or the government itself might want to consider participation in a global CT (e.g. WHO Solidarity trial). Factors the NRA must consider are the scientific merits of the trial design³ (14) [including the rapidity at which it generates quality data (9,17)], permission for import and GMP compliance status of the investigational product, and ethical rigor. The latter requires close coordination with the REC, using digital means as appropriate.



INNOVATIVE EXAMPLES OF CT REGULATION CAN BE FOUND ELSEWHERE IN THE WORLD. FOR EXAMPLE, AFRICAN COUNTRIES CONDUCT JOINT REGULATORY AND ETHICS REVIEWS OF MEDICINES AND VACCINES CTs AT THE CONTINENTAL LEVEL THROUGH A PROGRAM CALLED THE AFRICAN VACCINES REGULATORY FORUM (AVAREF) (18). THIS IS CONSISTENT WITH THE SUB-REGIONAL MODEL MENTIONED IN THE ETHICS REVIEW AND OVERSIGHT SECTION OF THIS DOCUMENT.

The NRA’s approach must move with greater speed in the receipt, screening, evaluation, review, and authorization of pandemic related CTs compared to normal circumstances. They can use the recommendations and strategies for expediting review mentioned in the REC section, such as digital documentation, virtual meetings, tight timeframes, fee waivers or reductions, and decision delegation to the science leads within the agency rather than the Head of Agency or Minister for each trial.

³ Hierarchy of trial designs: meta-analyses of good quality randomized controlled clinical trials showing consistent results; individual randomized controlled trials; meta-analysis of observational studies; individual observational studies; published case reports; anecdotal case reports; expert opinion on the matter.

Further, the NRA can prioritize existing resources for pandemic-related CTs. For example, the US Food and Drug Administration has created a special emergency program called the Coronavirus Treatment Acceleration Program (CTAP). CTAP uses multiple strategies to increase the resources allocated to the review of the CT, including redeploying staff to focus on pandemic-related CTs, involving senior management in decision-making to elevate the level of priority, redeploying other medical and policy staff to support these efforts, and implementing streamlined processes for developers, providers, and researchers to send inquiries and requests.

Ongoing Oversight

After approval and prior to enrolling the first research participant, the trial must be registered in a registry that is part of ICTRP. In addition, the NRA must continue to prioritize COVID-19 trials, including monitoring of the CT throughout its lifecycle. This requires continued coordination with the REC, which will be evaluating any changing ethical scenarios based on emerging evidence. Also, the NRA must have the authority to receive notifications of changes to the CT from the investigators as the trial progresses (4). Additionally, the NRA must also have the right to conduct inspections at the different trial sites to ensure compliance with GCP, or, at least, agree on the means for conducting these inspections virtually due to pandemic considerations. Maintaining regular official conversations between the NRA and trial sponsors is highly advisable. The NRA must also receive reports of adverse events that occur during the trial and evaluate them accordingly. Many COVID-19 patients are advanced in age, with multiple comorbidities, and take numerous medicines that could interact with the interventions under study. The NRA must have the ability to suspend or stop trials that do not comport with standards or that raise unacceptable risks to those involved in the CT, including study participants, as well as researchers and staff.

Results Submitted for Marketing Authorization, Import Permit, Procurement

Finally, if the results of the CT are submitted to the NRA in an application for marketing or use authorization during the pandemic, the government should use reliance on a reference authority's evaluation of the CT and overall emergency use authorization (EUA) of the product, per PAHO guidance (19). This procedure departs from standard processes given the urgency of pandemic situations.

Oversight of CTs unrelated to the COVID pandemic

It is also necessary to consider how CTs that are not related to the pandemic are conducted during the pandemic. Challenges may arise from quarantines, site closures, travel limitations, supply chain disturbances, and risk of site personnel or trial subjects contracting and/or spreading COVID-19 (20). Protocol modifications may be needed, and sponsors must describe these contingency measures to the NRA, including participants affected, and provide analyses and discussions of any impacts on the CT (21-28).

Emergency Use of Unproven Interventions Outside of Research

The absence of safe and efficacious therapeutics for COVID-19 has led to discussions about the emergency use of unproven interventions outside of research protocols with human subjects. Given the urgency to produce evidence about the safety and efficacy of interventions to treat or prevent COVID-19, it is critical to conduct research capable of yielding that evidence as quickly as possible, such as multisite, well-conducted, blinded, randomized CTs. However, as in previous emergencies, NRAs are faced with requests to provide interventions that are not proven effective or safe for COVID-19 outside

of research protocols, sometimes invoking the logistical challenges involved in conducting CTs as an obstacle.

Such emergency use of unproven interventions might be ethically justified in the context of COVID-19. WHO has specified the conditions under which this “monitored emergency use of unregistered and experimental interventions” (MEURI) is ethical:

1. No proven effective treatment exists;
2. It is not possible to start clinical studies immediately;
3. Preliminary data on safety and efficacy justify the intervention, and its use outside of a trial has been suggested by scientific committee;
4. Use under MEURI is approved by NRAs, other relevant health authorities and a REC;
5. Resources to minimize risks are available;
6. Patients provide their informed consent;
7. The use is monitored, and results are documented and shared in a timely manner (29).

Emergency use of unproven interventions under these conditions may contribute to the generation of weak evidence while ensuring adequate oversight and allowing access to interventions that *may* be beneficial. The ethical framework of MEURI relates to regulatory categories usually called “expanded access”⁴ or “compassionate use,” which are subject to specific constraints (that may vary among themselves and with WHO’s ethics guidance) in each jurisdiction. In line with the requirements for ethical use of unregistered interventions in emergencies, their use as part of protocols and programs for expanded access, with some procedures and mandatory requirements to be fulfilled, is notably preferable over single-patient uses because they allow for data collection in a more systematic and efficient manner. Furthermore, emergency use of unproven interventions does not impede the implementation and completion of adequate and well-controlled clinical trials of the product’s use treating COVID-19 patients.

It must however be highlighted that these interventions have not been tested yet and their benefit-risk profile is unknown. Extreme caution and clear communication to the public is needed for transparency and to avoid promoting false expectations. Certainly, some unproven interventions have a more plausible positive risk-benefit profile (e.g. convalescent plasma) and there are stronger justifications for their use outside of CTs. However, this use must not come at the expense of compromising efforts or resources to conduct CTs, which produce evidence quicker and provide the scientific basis for the authorization of and appropriate use of new drugs. For these reasons, it is advisable to encourage the use of interventions that are unproven for COVID-19 in the context of CTs to the extent that it is possible.

Conclusions

⁴ According to NYU Langone Health’s Working Group on Compassionate Use & Preapproval Access Frequently Asked Questions, “compassionate use,” “expanded access,” “preapproval access,” and “right to try” are terms that generally refer to the use of a medical product, for therapeutic benefit, that hasn’t been approved for sale or marketing by the country’s regulatory authority (the U.S. regulatory authority is the Food and Drug Administration, or FDA).

PAHO recommends that countries put in place the ML1 and ML2 capacities indicated by the WHO GBT for CT regulation, including special provisions for CT oversight in the context of the COVID-19 pandemic. More specifically:

- NRAs, RECs and all relevant parties must commit to ensuring adherence to ethical and regulatory standards for the review and oversight of COVID-19 CTs while adjusting processes and advancing coordination as recommended to catalyze the production of the evidence that is urgently needed.
- Although there are specific conditions under which the use of unproven interventions under regulatory categories such as “expanded access” and “compassionate use” can be ethical in the context of the pandemic, they must not come at the expense of compromising efforts or resources to conduct CTs, which produce evidence quicker and provide the scientific basis for the safe and efficacious use and authorization of new interventions. Therefore, the use of unproven interventions for COVID-19 must be strongly encouraged to occur in the context of CTs.

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