Guidance on ethical and regulatory preapproval of research for health emergencies

Introduction

Research is an essential component of preparedness for and response to health emergencies. Producing high-quality knowledge in a timely manner makes it possible to identify safe and effective interventions to protect the population's health and well-being and to guide public health measures in response to emergencies (1, 2).

During the COVID-19 pandemic, the Region of the Americas responded rapidly to the need to produce knowledge: a large number of studies on COVID-19 were conducted, regulatory frameworks were adapted to accelerate research ethics oversight processes, and measures were adopted to promote research transparency. However, significant challenges persisted, including the lack of coordination and collaboration mechanisms for developing scientifically rigorous research and limited capacity to lead high-impact studies (1, 3).

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Building on this experience and the lessons learned, the Pan American Health Organization (PAHO) has been working with the various stakeholders involved in research to strengthen the Region's preparedness for future emergencies. This work goes beyond strengthening the capacities needed to respond when an emergency occurs; it also includes actions aimed at undertaking, during non-emergency periods, everything that can be done in advance to facilitate rapid, rigorous research in accordance with international standards once an emergency has begun (3–6).

This preparedness is particularly relevant because some research can only be conducted during very brief periods, when the necessary epidemiological conditions arise. Outbreaks of certain diseases can be unpredictable and short-lived, so waiting for an outbreak to occur before beginning to develop research protocols and carry out ethics review and, where applicable, regulatory review may mean losing the opportunity to conduct research of great social value. Experiences with emergencies in the Region, such as those caused by the Zika, Chikungunya, and Oropouche viruses, have highlighted this challenge: research initiated as prospective studies could not be completed or had to be converted into retrospective studies because protocol development and approval took so long that, by the time participant recruitment began, the virus was no longer circulating.

Research preapproval seeks to prevent these problems. It will therefore help close a gap in health emergency preparedness by enabling research to begin with the necessary speed as soon as conditions allow. Having preapproval processes makes it possible to advance ethics review and, where applicable, regulatory review of research before an emergency, so that when an outbreak or emergency occurs, preapproved protocols are available that can quickly be completed and adapted to the specific circumstances. The value of these processes therefore lies not only in expediting ethical

and regulatory reviews and reducing the workload of those conducting them during outbreaks or health emergencies. Preapproval processes also help expand opportunities to develop and conduct research during outbreaks or health emergencies that addresses the health needs and priorities of countries in the Region and that might otherwise not be carried out.

Regional background

The possibility of developing research protocols and reviewing them in advance has gained prominence in the Region as part of preparedness for future emergencies. During the Zika outbreak, the urgent need to produce knowledge rapidly led PAHO, in collaboration with various researchers in the Region, to develop standardized protocols to facilitate research (7, 8). However, this effort began after the outbreak had started, leaving no opportunity to consider preapproval of these protocols. Subsequently, in response to the epidemic of chronic kidney disease in agricultural communities in Central America, PAHO developed master protocols to facilitate rigorous research in different countries in the Region, which were preapproved by the PAHO Ethics Review Committee (PAHOERC) (9, 10).

The COVID-19 pandemic once again demonstrated the importance of being prepared to conduct high-quality research rapidly and renewed the discussion of the usefulness of having research protocols reviewed in advance. Drawing on lessons learned during the pandemic, PAHO identified the need to advance the development of preapproved protocols as part of the Region's pending agenda for preparedness for future emergencies. In particular, it recommended that the scientific community, international organizations, and health authorities develop research protocols for potential emergencies in advance and submit them to preliminary ethics review, so that, when an emergency occurs, they can be adapted to the specific context and their final versions reviewed and approved rapidly (1).

Within this framework, PAHO, in collaboration with CEPI, conceived the preapproved protocols project, which is part of the Clinical Trials Accelerator initiative (11). This project aims to facilitate the initiation of research during outbreaks and health emergencies, especially when the window of opportunity to generate valuable knowledge is very short.

Objective

This guidance aims to define the processes for ethical preapproval and final ethical approval and, where applicable, regulatory preauthorization and final regulatory authorization of health-related research, in order to facilitate its timely initiation during outbreaks and health emergencies. The aim is to enable a substantial part of the work involved in preparing and reviewing research protocols and other study documentation to be carried out before an emergency, without reducing the rigor of ethics or regulatory review, or compromising or replacing the final approvals required to begin any research involving human participants.

Scope

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This guidance covers two areas of research review. The first encompasses ethical preapproval and final ethical approval processes carried out by duly accredited research ethics committees (RECs). The second encompasses regulatory preauthorization and final regulatory authorization processes conducted by national regulatory authorities (NRAs). This distinction reflects the differences between ethics oversight and regulatory oversight of research.

Ethics oversight covers all health-related research involving humans and is the responsibility of RECs, which review and monitor research in accordance with the international ethical standards established in the International Ethical Guidelines for Health-related Research Involving Humans of the Council for International Organizations of Medical Sciences (CIOMS) (12). Regulatory oversight, in turn, is the responsibility of NRAs, which oversee clinical trials with medicines, vaccines, medical devices, and other health technologies that require regulatory authorization, in accordance with the Good Clinical Practice (GCP) guidelines of the International Council for Harmonisation (ICH) (13, 14).

Thus, while ethics oversight applies to all health-related research involving humans, only a subset of clinical trials also requires regulatory oversight by NRAs. Consequently, the ethical preapproval and final ethical approval processes proposed in this guidance may be applied to all health-related research involving humans, while regulatory preauthorization and final regulatory authorization processes will also be required for clinical trials subject to NRA oversight.

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General characteristics

This guidance proposes dividing research review processes into two stages: reviewing before an emergency everything that can reasonably be reviewed with the available information, and completing the review once the emergency occurs and the necessary specific information becomes available. This approach does not alter the applicable international ethical or regulatory standards; rather, it allows research reviews to move forward ahead of time and, consequently, expedites final approval processes. It is therefore a procedural proposal intended to facilitate the timely initiation of research during health emergencies. Together, the two stages must ensure compliance with the same requirements and standards that would apply if the entire review process were carried out after the emergency occurred.

A central feature of this guidance is to allow a research package that does not yet contain all the necessary information necessary (an “noncomplete protocol”) to be submitted for ethics review and, where applicable, regulatory review before an outbreak or health emergency occurs, in order to obtain ethical preapproval and regulatory preauthorization, respectively. Once the outbreak or emergency occurs, the research submission package must be completed with context-specific information and may undergo an accelerated review to obtain final ethical approval and, for clinical trials within the remit of NRAs, final regulatory authorization (Figure 1). Where applicable, ethical and regulatory reviews should be conducted in parallel, both during the preapproval and preauthorization stage and during the final approval and authorization

stage. It is important to emphasize that neither ethical preapproval nor regulatory preauthorization allows research to begin. Research may begin only after final ethical approval has been obtained and, for clinical trials within the remit of NRAs, final regulatory authorization has also been obtained.

Key concepts

The protocol and its noncomplete status

Because this guidance addresses both ethical and regulatory review processes, and solely for the purposes of this guidance, the term "*protocol*" (in italics) will be used broadly to refer to the set of documents comprising the research package submitted for ethics review and, where applicable, regulatory review. This research submission package includes the *protocol* itself and accompanying documentation, such as informed consent documents and data collection instruments. For clinical trials within the remit of NRAs, the *protocol* should be understood, for the purposes of this guidance, to also encompass all documentation and information included in a regulatory submission package in accordance with GCP, such as the investigator's brochure and documentation relating to the investigational product.

A *protocol*'s "noncomplete" status refers exclusively to information that cannot be known or determined before an emergency or outbreak occurs and that can therefore only be incorporated later (for example, the specific sites where the study will be conducted, the epidemiological characteristics of the outbreak, or the specific population that will participate in the research). It is not possible to establish a predetermined list of all the elements an noncomplete *protocol* must contain, since very different studies and scenarios can be envisaged in which different *protocol* components may be absent. Nevertheless, the starting point is the *protocol* components normally required for any research submitted for ethics review and, where applicable, regulatory review. To initiate the preapproval process, these requirements must serve as the basis, and the absence of any elements that cannot be completed ahead of time must be justified. In other words, the *protocol* must be submitted with all the elements normally required (12, 13), except those that cannot reasonably be known because they depend on the characteristics of the future emergency or outbreak, and their absence must be explicitly justified.

Preapproval

Preapproval is the outcome of reviewing an noncomplete *protocol* ahead of time, during non-emergency periods, before an outbreak or health emergency occurs. This advance review is no less rigorous: it is governed by the international standards applicable to research involving human participants. Its distinguishing feature is that it evaluates those aspects of the noncomplete *protocol* for which sufficient information is available, while leaving pending or unfinished the evaluation of aspects that can only be determined once the outbreak or emergency occurs.

This guidance uses "ethical preapproval" to refer to the decision issued by a REC following advance ethics review, and "regulatory preauthorization" to refer to the decision issued by an NRA following advance regulatory evaluation. Neither decision

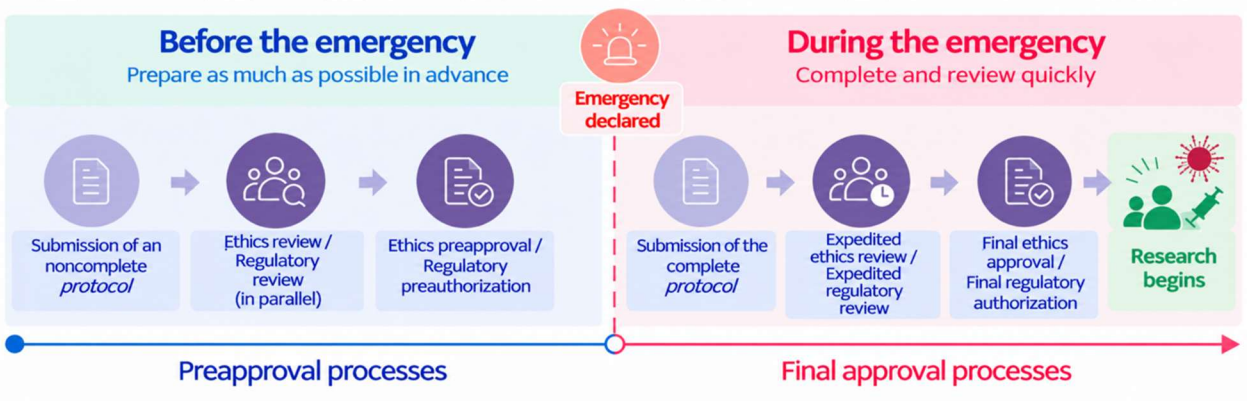
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guarantees automatic final ethical approval or regulatory authorization, nor does either permit research to begin. Once the outbreak or emergency occurs and the necessary information is available, the *protocol* must be completed and submitted for the relevant reviews to obtain final ethical approval and, where applicable, final regulatory authorization.

Outbreaks or health emergencies

For the purposes of this guidance, outbreaks or health emergencies are understood as situations that pose a significant threat to the population's health and require a timely public health response, including the generation of knowledge to guide the necessary decisions and interventions. These situations may be local, subnational, national, regional, or international in scope and may include infectious disease outbreaks, epidemics, pandemics, emergencies arising from natural disasters, or other public health events. They are not limited to public health emergencies of international concern (PHEICs) as defined in the International Health Regulations (IHR) (15); however, they must be outbreaks confirmed or emergencies declared by the competent health authorities.

Figure 1. Preapproval and final approval processes



I. Ethics review processes

Implementing ethical preapproval and final ethical approval requires RECs to expressly include these processes in their standard operating procedures (SOPs). These procedures should establish how ethics review will be carried out at each stage, in accordance with this guidance (Figure 2). Likewise, national bodies responsible for REC oversight should, where applicable, include these processes into committee accreditation criteria as part of the SOPs for research ethics oversight in health emergencies (16).

Figure 2. Ethical preapproval and final ethical approval process



a) Ethical preapproval process

The ethics review process for a *protocol* submitted for preapproval is the same as the process a REC would carry out for any research. There is therefore no need to convene extraordinary meetings or modify quorum requirements for decision-making, as is necessary during a health emergency. The distinguishing feature of this first review stage is that the *protocol* submitted to the REC does not yet contain all the information necessary to conduct the research, since certain study elements can only be defined once an outbreak or emergency occurs, such as the epidemiological context, the location where the research will be conducted, or the specific characteristics of the participant population.

Researchers are responsible for explicitly justifying the absence of information in the *protocol*. They must explain why it cannot be determined in advance, and justify the need to submit the *protocol* for ethical preapproval in light of its relevance to responding to potential outbreaks or emergencies and the social value of the knowledge expected to be generated. Based on this information, it is recommended that the REC meet with the researchers to discuss aspects of the *protocol* requiring further analysis, issues that can be resolved in advance, and those that will need to be addressed during the final ethical approval stage.

The REC's ethical analysis is based on the same international ethical standards set out in the CIOMS Ethical Guidelines that apply to any research involving human participants (e.g., the social value and scientific validity of the research, fair participant selection, or the informed consent process) (12). However, analysis of some of these criteria may be not conclusive because information needed to determine the study's ethical acceptability is lacking. Ethical deliberation may also enable the REC to anticipate potential ethical challenges that could arise in different scenarios and formulate recommendations for addressing them, to be considered once context-specific information becomes available. For example, conducting a cohort study during an mpox outbreak transmitted primarily among men who have sex with men will require additional measures to protect participants if the study takes place where such relationships are criminalized.

Following the relevant ethical analysis, the REC may decide to: a) request additional information, clarifications, or modifications to the submitted *protocol* before making a decision; b) grant ethical preapproval; or c) deny preapproval. Any of these decisions must be formalized in a document issued in accordance with the REC's SOPs.

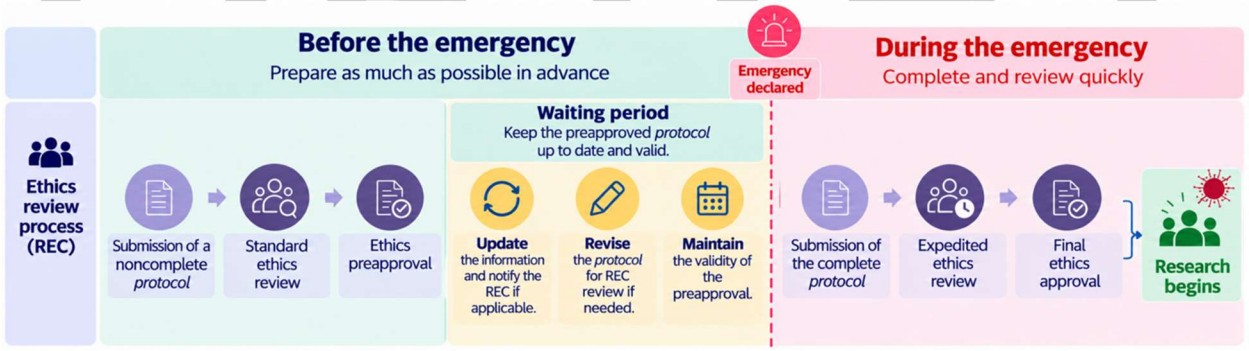
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When preapproval is granted, the document must specify that the study may not begin until final ethical approval has been obtained. It must also include comments, recommendations, and stipulations regarding aspects that researchers must consider once specific information on the outbreak or emergency becomes available and the missing *protocol* details or components can be completed. This REC guidance will help researchers complete the *protocol* and facilitate its subsequent review for final ethical approval. Finally, the preapproval document must establish the deadline by which researchers must submit the corresponding justification to keep the preapproval valid.

During the waiting period between ethical preapproval of the *protocol* and the outbreak or emergency in which the research is expected to be conducted, the preapproved *protocol* must be kept up to date and valid (Figure 3). If new evidence emerges or an event occurs during this period that could affect the conduct of the study (for example, new information on populations at risk or the availability of alternative treatments), researchers must promptly inform the REC and, where applicable, submit the necessary amendments for ethics review. The aim during this period is to maintain a "living" *protocol* so that, when the emergency occurs, the work carried out in advance remains valid and the *protocol* can be reviewed rapidly for final ethical approval.

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Figure 3. Ethics review process including a waiting period



b) Final ethical approval process

When an outbreak or emergency occurs in which a preapproved *protocol* is expected to be implemented, the *protocol* must be submitted to the relevant REC to obtain final ethical approval before the research can begin. Once the specific information that was unknown at the time of preapproval becomes available, researchers must incorporate it into the *protocol*. In doing so, they must consider the comments, recommendations, and stipulations included in the preapproval document issued by the REC.

Researchers must submit the complete *protocol* to the REC together with the preapproval document issued by the committee, clearly identifying information added or modified relative to the preapproved version (for example, through a track changes

system that makes the modifications visible). This will enable the REC to easily identify the aspects requiring review at this stage.

Since the *protocol* has already received preapproval, the review for final ethical approval will build on the REC's previous ethical analysis and deliberation. The review must therefore focus on new information incorporated into the *protocol* and on aspects for which a conclusive ethical analysis was not possible during preapproval and that were identified at that stage for subsequent consideration.

At this stage, ethics review must be conducted rapidly and rigorously, in accordance with the standard operating procedures (SOPs) established for research ethics oversight during health emergencies. Some of the topics to be included in these SOPs are (1):

- Electronic communications and submission of documentation.
- Flexible requirements for document submission.
- Virtual meetings.
- Asynchronous review and decision-making.
- Reduced quorum.
- Short timelines.
- Mechanisms for communication and coordination with researchers, health authorities, and NRAs, where applicable.
- Digital documentation records and archiving.

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Following the review and corresponding ethical analysis, the REC may: a) request additional information, clarifications, or modifications to the submitted *protocol* before making a decision; b) grant final ethical approval; or c) decline to approve the research. Any of these decisions must be formalized in a document issued in accordance with the REC's SOPs.

Final ethical approval is an essential requirement for initiating research.
It is important for the REC to maintain a collaborative relationship with researchers throughout the entire process: during preapproval, during the waiting period, and, once the emergency occurs, during the review for final ethical approval. This requires efficient, transparent communication mechanisms that facilitate timely information exchange and contribute to efficient ethics review processes.

II. Regulatory review process

Implementing regulatory preauthorization and final regulatory authorization processes for clinical trials involving health products subject to regulatory authorization requires NRAs to have a legal framework that expressly provides for these processes. As part of health emergency preparedness, NRAs must have regulatory provisions that allow them to adapt and expedite procedures for regulatory oversight of clinical trials without compromising ethical, quality, and safety standards (6). These provisions should require

parallel ethical and regulatory review, and allow the regulatory review of the *protocol* to be carried out ahead of time, and later completed once the emergency occurs, as described below (Figure 4).

Figure 4. Regulatory preauthorization and final regulatory authorization process



a) Regulatory preauthorization process

Before an outbreak or health emergency occurs, the sponsor may submit the noncomplete *protocol* to the competent NRA to request regulatory preauthorization. Although some trial-specific elements cannot yet be defined because they depend on the characteristics of the future outbreak or emergency (e.g., epidemiological characteristics), the documentation submitted in the clinical trial submission package must contain all information that can reasonably be determined in advance and enable a sufficiently comprehensive regulatory evaluation of aspects that do not depend on the emergency context (6).

As part of the preauthorization process, the NRA will review the noncomplete *protocol*, which should include regulatory support (6). This support will facilitate early dialogue between the NRA and the sponsor to discuss the documentation submitted for preauthorization (e.g., the potential development plan, aspects of the investigational product, nonclinical data, study design, endpoints, critical issues, or operational feasibility), examine the justification for preauthorization and for the missing elements in light of the available scientific evidence, and anticipate aspects that will need to be addressed once the outbreak or emergency occurs.

Once the regulatory review has been completed, the NRA may decide to: a) request additional information, clarifications, or modifications to the *protocol* before making a decision; b) grant regulatory preauthorization; or c) deny preauthorization. Any decision adopted by the NRA must be formalized in a document issued in accordance with its procedures.

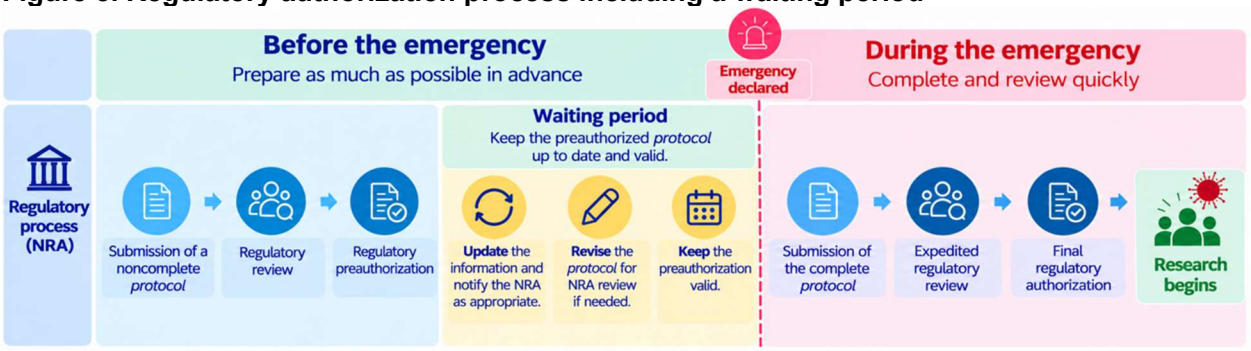
When preauthorization is granted, this document must record the documentation reviewed during this stage and include the recommendations and stipulations to be considered by the sponsor when requesting final regulatory authorization for the trial. Preauthorization does not permit the clinical trial to begin.

During the waiting period between trial preauthorization and the outbreak or emergency in which the study is expected to be conducted, the clinical trial submission package

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must be kept up to date and valid (Figure 5). If new evidence emerges or an event occurs during this period that could affect the conduct of the study (for example, new information on the investigational product or the availability of alternative treatments), the sponsor must promptly inform the NRA and, where applicable, submit the necessary modifications for regulatory review. In addition, the NRA must establish how frequently the clinical trial submission package is to be updated until the outbreak or emergency occurs. The aim during this period is to maintain a "living" submission package so that, when the emergency occurs, the work carried out in advance enables the *protocol* to reviewed rapidly for final regulatory authorization.

Figure 5. Regulatory authorization process including a waiting period



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b) Final regulatory authorization process

When an outbreak or health emergency occurs in which a clinical trial with regulatory preauthorization is expected to be conducted, the sponsor must complete and update the *protocol* with the specific information that was not available at the time of preauthorization. In doing so, the sponsor must consider the recommendations and stipulations established by the NRA in the preauthorization document.

Once the *protocol* is complete, the sponsor must request regulatory authorization for the clinical trial. The sponsor must clearly identify information added or modified relative to the documentation previously reviewed (for example, through a track changes mechanism that makes the modifications visible). This will enable the NRA to distinguish elements already reviewed from those requiring evaluation at this stage.

Since part of the regulatory review will have been carried out during preauthorization, the evaluation for final authorization must focus on new or modified information and on aspects that could not be comprehensively reviewed in advance. At this stage, the NRA must prioritize the evaluation of the preauthorized *protocol* and conduct it rapidly and rigorously, in accordance with the procedures established for emergency situations (6). These procedures must include measures such as the following to organize and expedite the review so that it can be completed within a shorter timeframe:

- Simplification of administrative procedures (for example, more flexible procedural requirements for document submission).
- Early assignment of reviewers with the necessary technical expertise.

- Criteria for prioritizing applications.
- Shortened timelines for evaluation and issuance of decisions.
- Mechanisms for ongoing interaction with sponsors (for example, virtual meetings and direct, frequent communication channels for technical queries) to identify and resolve issues arising during the review in a timely manner.
- Channels for communication and coordination with RECs to facilitate parallel ethical and regulatory review processes.

Following this evaluation, the NRA may: a) request additional information, clarifications, or modifications to the complete research package before making a decision; b) authorize the clinical trial; or c) decline to authorize it. Any decision adopted by the NRA must be formalized in a document issued in accordance with its procedures.

It is important for the NRA to maintain a collaborative relationship with all stakeholders involved in the study throughout the entire process: during preauthorization, during the waiting period, and, once the emergency occurs, during the review for final authorization. This requires efficient, transparent communication mechanisms that facilitate timely information exchange and contribute to efficient regulatory review processes (6).

Final regulatory authorization and final ethical approval are essential requirements for initiating a clinical trial that has been preapproved and preauthorized for implementation during an outbreak or health emergency.

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III. Challenges and other specific considerations

1. Why should RECs and NRAs preapprove protocols?

During emergencies, rapid but rigorous research reviews require considerable effort from research ethics committees (RECs) and national regulatory authorities (NRAs). Reviewing and preapproving *protocols* in advance will reduce the workload during emergencies and help ensure rigorous reviews, because it allows part of the work to be carried out during non-emergency periods and attention to focus on missing aspects during the emergency. Processes will thus be faster and less demanding for RECs and NRAs during the emergency. Moreover, some research essential for responding to emergencies that may affect our populations can only be conducted if preapproval processes are in place to enable studies to take place within the brief window of opportunity available. As countries in the Region of the Americas strengthen their capacity to lead research that addresses our population's health needs, it is imperative to create conditions that ensure this research has the greatest possible impact. Having research preapproval procedures will improve our emergency preparedness, optimize the use of resources, and prevent the loss of valuable opportunities to generate knowledge that helps protect the population's health and well-being.

2. Is preapproval sufficient to facilitate research during outbreaks and health emergencies?

No. Preapproval is an important strategy for strengthening research preparedness for outbreaks and health emergencies, but it is only one element in a broader set of actions needed to facilitate timely research. These include identifying research priorities in advance, strengthening research capacities—including ethical and regulatory oversight—allocating resources to fund research, establishing coordination and collaboration mechanisms among stakeholders, and establishing ethics oversight strategies to avoid repetitive research review during emergencies.

Preapproval contributes to this effort by allowing a substantial part of the ethics review and, where applicable, regulatory review of research to be carried out in advance, but its implementation must be integrated with other actions so that research can begin rapidly during emergencies. Furthermore, establishing preapproval processes will have the desired impact only if accompanied by the development of *protocols* for preapproval, a task for researchers, sponsors, health authorities, and international organizations.

3. How can we integrate preapproval into strategies for organizing ethics oversight in health emergencies?

To avoid multiple rapid reviews and duplication of effort, competent authorities must establish, as part of health emergency preparedness, the organizational strategy (or combination of strategies) for research ethics oversight in emergencies that best suits their context (e.g., an ad hoc committee, national-level committee, extraterritorial committee, or provincial or subnational committee) (1). Once the strategy has been defined, the RECs competent to oversee research in emergency situations—including reviewing preapproved *protocols* for final approval—must have rapid, flexible SOPs that enable rigorous and efficient operation (Figure 6).

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Figure 6. Approach to research ethics oversight in emergencies:
Step 1 → The competent authorities define the national strategy for organizing research ethics oversight in emergencies (e.g., an ad hoc committee, national-level committee, extraterritorial committee, or provincial or subnational committee, among others).

Step 2 → The competent RECs, in accordance with the established strategy, must have rapid, flexible SOPs that ensure rapid, rigorous ethics reviews of research and efficient monitoring.

4. What should RECs' SOPs for ethics review in emergencies look like?

Annex 1 of PAHO's publication Catalyzing ethical research in emergencies. Ethics guidance, lessons learned from the COVID-19 pandemic, and pending agenda contains a template of SOPs for ethics oversight of research related to health emergencies that RECs may freely use (1).

5. What happens if different RECs are involved in preapproval and final ethical approval?

The REC that granted preapproval for a *protocol* may not be the same REC that has the authority to review research in emergency situations. For example, a country may have established, as its national ethics oversight strategy, that an ad hoc REC is responsible

for reviewing and monitoring research conducted during emergencies. In such cases, the preapproved *protocol* should, in principle, be submitted to a different REC—the ad hoc REC—to obtain final ethical approval.

However, there is no single way to address this challenge. The key is to avoid unnecessary duplication of effort and ensure that review during the emergency can be conducted rapidly and rigorously. For example, when the REC competent to grant final ethical approval differs from the one that granted preapproval, mechanisms for communication and cooperation between them should be established. Another option would be for members of the REC that granted preapproval to participate in the review for final ethical approval. Alternatively, the national strategy could allow RECs that have preapproved a *protocol* to retain the competence to review it and grant final ethical approval, even when another mechanism has been established for ethics oversight of research during the emergency.

6. What should a REC consider when establishing the validity period of an ethical preapproval?

The REC must establish the validity period of ethical preapproval taking into account the specific characteristics of each study. Factors it could consider include the nature of the study, the characteristics of the populations expected to be recruited, the risks involved, the available scientific evidence and how it may evolve, and local epidemiological conditions. During this period, researchers must keep the *protocol* up to date and inform the REC of any new information or modifications that could affect the preapproval granted. Where applicable, the REC must determine whether these changes require a new review or a modification of the preapproval conditions.

7. How can different RECs in the Region collaborate during ethical preapproval and final ethical approval processes?

RECs can collaborate by exchanging information and experiences regarding ethical preapproval and final ethical approval processes for research. To this end, it is recommended that information on preapproved *protocols* be publicly available, enabling other RECs to learn about studies reviewed in advance and facilitating coordination when research is expected to be conducted in different locations across the Region.

It is also important to establish communication channels among RECs to share information on the reviews conducted, comments and recommendations made, and ethical challenges identified. This collaboration can help avoid unnecessary duplication of effort, promote consistency among ethics reviews, and facilitate the timely conduct of multicenter research during outbreaks and health emergencies. The national authority responsible for accrediting and overseeing RECs plays a central role in establishing coordination mechanisms among them.

8. What do NRAs need to effectively implement clinical trial preauthorization and authorization processes?

NRAs must have a legal framework that expressly grants them the authority to preauthorize and authorize clinical trials related to health emergencies, and to establish

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and implement the regulatory actions necessary for this purpose (for example, parallel research reviews by RECs and NRAs, criteria for prioritizing studies, accelerated review procedures during emergencies, and requirements for importing and labeling investigational products). These actions are part of a broader set of measures that NRAs should implement for regulatory oversight before and during emergencies. They also include mechanisms for ongoing study monitoring, inspections adapted to the emergency context, provisions for implementing decentralized elements, communication strategies and early regulatory support, and mechanisms for regulatory cooperation and reliance (6).

9. How can different NRAs in the Region collaborate during regulatory preauthorization and authorization processes?

NRAs can collaborate through regulatory reliance mechanisms, which allow an authority to consider the evaluations and decisions of other NRAs as a basis for its own review and authorization processes. These mechanisms can apply both to reviews conducted during preauthorization and to those for final regulatory authorization.

NRAs may also apply regulatory reliance mechanisms to decisions on safety measures for the investigational product, as well as to inspection findings and good manufacturing practice (GMP) certifications issued by other authorities, where applicable. This collaboration can help avoid unnecessary duplication of reviews, optimize the use of regulatory resources, and facilitate timely authorization of clinical trials during outbreaks and health emergencies.

10. How should regulatory review be coordinated with ethics review during research preapproval and final approval processes?

When research requires both ethics review and regulatory review, the two processes should be conducted in parallel, both during preapproval and preauthorization and during final approval and authorization. To this end, RECs and NRAs should establish coordination mechanisms and communication channels in advance that allow timely exchange of information on reviews conducted, comments made, and issues awaiting resolution. These mechanisms should facilitate the identification and joint resolution of issues requiring the involvement of both bodies, as well as coordination of review timelines and the issuance of decisions.

11. What operational measures should be considered during the waiting period to facilitate the conduct of research?

During the waiting period, researchers and sponsors, as appropriate, should advance, as far as possible, the planning and preparation of operational aspects needed to facilitate the timely initiation of research when an outbreak or health emergency occurs. These measures may include identifying potential research sites and investigators who would participate in the study, planning the necessary staff training, preparing contracts with participating institutions and investigators (3), and establishing agreements or arrangements with service providers needed to conduct the study. For clinical trials, consideration should also be given to obtaining insurance policies, developing risk

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management plans, and planning in advance for the availability of investigational products and supplies needed to carry out the study (6).

Advancing preparation of these aspects makes it possible to identify and address potential operational difficulties before an emergency occurs, reducing the likelihood of delays in initiating research once the corresponding final ethical and regulatory approvals have been obtained.

12. How can transparency in preapproved protocols be advanced?

To promote transparency, it is recommended that national research registries include *protocols* that have obtained ethical preapproval and, where applicable, regulatory preauthorization. This will make it possible to identify studies that has been reviewed in advance, the status of review and approval processes, and the institutions that are responsible for the studies.

PAHO will also promote the establishment of a regional registry of preapproved *protocols* that enables researchers, sponsors, RECs, NRAs, and other interested stakeholders to consult this information. This registry will help raise the visibility of studies developed ahead of time in the Region, facilitate information exchange, and encourage coordination and collaboration among countries for its potential implementation during outbreaks and health emergencies.

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13. How can society be involved in protocol preapproval and final approval processes?

Early and sustained engagement of potential participants, their communities, and the general public is essential to promote transparency, encourage participation, strengthen trust in research, and help ensure that studies address populations' needs and priorities (1, 12). Preapproval processes offer an opportunity to begin this engagement before an outbreak or health emergency occurs, allowing more time to establish mechanisms for dialogue, identify concerns, and plan participation and communication strategies.

This engagement may include consultations on the relevance of the research, identification of potential barriers to participation, and planning mechanisms to communicate study progress and results. During the waiting period, efforts should be made to maintain the dialogue established and, once the outbreak or emergency occurs, adapt engagement strategies to the characteristics and needs of affected communities. Advance work does not replace engagement during the emergency; it facilitates its continuity and adaptation to the specific context.

14. What should health authorities do to maximize the impact of preapproval as a strategy for preparedness for and response to outbreaks and health emergencies?

Health authorities should be aware of *protocols* that have obtained ethical preapproval and, where applicable, regulatory preauthorization, given their potential to generate relevant evidence for responding to an outbreak or health emergency. To this end, they

can consult existing public registries of preapproved *protocols* and maintain communication channels with researchers, sponsors, RECs, and NRAs.

When an outbreak or emergency occurs, health authorities should promote the implementation of relevant preapproved *protocols*. This entails encouraging and supporting researchers and sponsors to complete the *protocols* with context-specific information and submit them for final ethical approval and, where applicable, final regulatory authorization, so that research can begin once the required approvals have been obtained.

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