



CATALYZING ETHICAL RESEARCH IN EMERGENCIES

Ethics guidance, lessons learned from the COVID-19
pandemic, and pending agenda

PAHO



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Washington, D.C., 2022

Catalyzing Ethical Research in Emergencies. Ethics Guidance, Lessons Learned from the COVID-19 Pandemic, and Pending Agenda

ISBN: 978-92-75-12848-0 (PDF)

ISBN: 978-92-75-12849-7 (Print version)

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Suggested citation: Pan American Health Organization. Catalyzing Ethical Research in Emergencies. Ethics Guidance, Lessons Learned from the COVID-19 Pandemic, and Pending Agenda. Washington, D.C.: PAHO; 2022. Available from: <https://doi.org/10.37774/9789275128480>.

Cataloguing-in-Publication (CIP) data: Available at <http://iris.paho.org>.

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HSS/BIO/2022

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ACKNOWLEDGMENTS

This publication was prepared by the Regional Program on Bioethics, which is part of the Department of Health Systems and Services of the Pan American Health Organization (PAHO), under the general coordination of Carla Saenz. Sarah Carracedo, Ana Palmero, and Carla Saenz were in charge of the writing.

PAHO gratefully acknowledges the contribution of all the participants in the regional dialogue sessions, whose reflections and suggestions constitute a key component of this work. PAHO further acknowledges and thanks the advice of the expert group comprised by Bernardo Aguilera, Florencia Luna, Sofia Salas, Sergio Surugi de Siqueira, Hans Vasquez and Argentina Ying. At first, Ricardo Palacios was also part of the group. The publication benefited from the review and technical contribution of Ludovic Reveiz, Marcie Neil, Lionel Gresh, and Ian Stein.

This publication was developed by PAHO with the financial support of the Wellcome Trust grant 220028/Z/19/Z.

INTRODUCTION

Health research has attracted more attention than ever during the COVID-19 pandemic. Indeed, the pandemic has made it clear that research is an essential component of preparedness and response to health emergencies. For this reason, it is urgent to catalyze research capable of producing safe and effective interventions for COVID-19 and to generate the knowledge needed to respond to the emergency. The urgency to conduct research does not, however, grant a license to deviate from ethical standards. On the contrary, all research related to health emergencies must adhere to the international ethical guidelines for health-related research involving humans prepared by the Council for International Organizations of Medical Sciences (CIOMS) ([1](#)), which include the scientific rigor that is indispensable for research to produce knowledge and achieve its proposed objectives.

Ensuring that all research is conducted ethically is fundamental to generating the population's trust in research and its results, as well as in health professionals and public health authorities. In a health emergency this trust is key, because the population's compliance with public health measures to a large extent depends on it; and compliance, in turn, is indispensable for reaching public health objectives. Furthermore, the COVID-19 pandemic has revealed that trust in public health interventions depends in many cases on trust in the research that proved the safety and efficacy of those interventions. This was the case with vaccines, for example.

The Regional Program on Bioethics of the Pan American Health Organization (PAHO) has developed ethics guidance documents for research in the context of the COVID-19 pandemic ([2](#), [3](#), [4](#), [5](#), [6](#), [7](#)), building on the experience of previous emergencies –including the Zika outbreak, for which PAHO also produced ethics guidance ([8](#))– , and the commitment of PAHO's Member States to strengthen ethics preparedness in emergencies ([9](#)). These guidance documents have been implemented rapidly ([10](#)) and have generated a regional learning process encouraged by numerous dialogue sessions involving health authorities, research ethics committees (RECs), and researchers from Latin American and the Caribbean (box 1). These dialogue sessions have become a forum for regional reflection on the measures that have worked and the aspects that continue to present challenges, what should be done differently –both in ordinary and emergency situations– and what issues are part of our regional agenda in preparation for future emergencies.

In this context, the aim of this publication is to offer a revised and integrated version of the ethics guidance documents for research in emergency situations previously developed by PAHO, and to supplement this with lessons learned in the Region during the COVID-19 pandemic. It also offers general recommendations that resulted from the regional dialogues, with the ultimate goal of catalyzing ethical research for health emergencies that may occur in the future.

Box 1. Regional dialogue sessions from Latin America and the Caribbean held by the Pan American Health Organization

Challenges and lessons to be learned in Latin America and the Caribbean: Regional dialogues on research ethics during the pandemic

- Strategies for ethics review and oversight of research during the pandemic [YouTube]. Washington, D.C.: PAHO; 2020. Available from: <https://youtu.be/QEreUcS96t4>
- REC Procedures [YouTube]. Washington, D.C.: PAHO; 2020. Available from: <https://youtu.be/WupmvjesdDQ> (No English translation available).
- Social and scientific value, and informed consent [YouTube]. Washington, D.C.: PAHO; 2020. Available from: <https://youtu.be/za5KGvx0nlg>
- The perspective of researchers [YouTube]. Washington, D.C.: PAHO; 2020. Available from: https://youtu.be/vD_V37yDw6A
- The risk-benefit assessment of studies [YouTube]. Washington, D.C.: PAHO; 2020. Available from: <https://youtu.be/HYQ7AJvUIDc>
- What have we learned so far? [YouTube]. Washington, D.C.: PAHO; 2020. Available from: <https://youtu.be/f3TY3vkWE9g>

Indicators for strengthening national research ethics systems: Series of regional sessions

- PAHO's indicators for strengthening national research ethics systems [YouTube]. Washington, D.C.: PAHO; 2021. Available from: <https://www.youtube.com/watch?v=-k5L3wHNmKO>
- Regional assessment using the indicators: Achievements and pending challenges [YouTube]. Washington, D.C.: PAHO; 2021. Available from: <https://www.youtube.com/watch?v=rszaSOCY63M>
- Regional assessment of the indicator on research in emergencies: Progress during the pandemic [YouTube]. Washington, D.C.: PAHO; 2021. Available from: https://www.youtube.com/watch?v=86Essklfc_c

Catalyzing ethical research in emergencies: Regional dialogues on the lessons learned from the COVID-19 pandemic and pending agenda

- Reflection and discussion on the preliminary recommendations [YouTube]. Washington, D.C.: PAHO; 2022. Available from: <https://youtu.be/tOs7z-BHsMI>
- Presentation of the revised recommendations and pending agenda [YouTube]. Washington, D.C.: PAHO; 2022. Available from: <https://www.youtube.com/watch?v=j2QOQJaoZjQ>

REC: Research ethics committee

CHAPTER 1.

LESSONS LEARNED FROM THE ZIKA OUTBREAK AND CHALLENGES DURING THE COVID-19 PANDEMIC

In 2016, the Region of the Americas experienced a public health emergency of international concern: the Zika virus outbreak. This emergency posed similar challenges to those experienced in previous emergencies due to a lack of clarity about the ethical standards that guide research in emergency situations. Questions arose about whether it was ethically acceptable to conduct research during emergencies, whether it was appropriate to ignore the usual ethical standards (such as obtaining ethics review prior to the initiation of a study or conducting informed consent processes), or whether it was acceptable to modify ethics review processes with the aim to speed up the review. The development of specific ethics guidance (8) and the strengthening of regional capacities made it possible to address those issues, which have not been subject of discussion during the COVID-19 pandemic.

Learning from the Zika outbreak led to the following points of consensus:

- research is an essential component of the response to health emergencies;
- research conducted in emergencies must adhere to international ethical standards, including prior ethics approval by a REC and informed consent of participants; and
- ethics review processes must be modified in emergency situations to ensure the rapid and rigorous review of research.

This learning was also encouraged by the publication of various guidance documents that address the ethical issues that arise when conducting research during public health emergencies (1, 11, 12, 13). Subsequent regional reflection led to PAHO's Member States committing to improve their ethics preparedness for future emergencies (9), including outbreaks and natural disasters. For this purpose, PAHO's research ethics indicators included an indicator measuring the number of countries that have established procedures for thorough accelerated ethics review of research during emergencies (14, 15). In 2018, when PAHO and Member States began the work of outlining and formalizing these procedures, there was no clarity at the global level on how exactly these rapid ethics review processes should be (1). Detailed and specific ethics guidance was needed to adapt relevant regulations. Accordingly, the measures taken in the Region to facilitate the rapid review of research in emergency situations before the COVID-19 pandemic were still mostly general in nature. (16).

When SARS-CoV-2 began to spread, the Region of the Americas was notably better prepared than when the Zika outbreak occurred. It was evident, however, that some challenges remained. Greater clarity on the relevant ethics guidance did not necessarily imply that there would be no challenges in putting this guidance into practice. For example, clarity that research with human participants in emergencies requires prior ethics approval from a REC does not imply that it is always simple to distinguish between which initiatives constitute research with human participants, and which constitute surveillance or other public health activities (box 2).

Box 2. How is research distinguished from public health activities that involve data collection?

Not all activities involving systematic data collection constitute research with human subjects. The difference between public health research and public health activities, such as surveillance, lies in their objective. Research has the primary objective of producing generalizable knowledge. While health authorities often engage in the conduct of research, they also systematically collect and analyze personal data that are primarily for the direct benefit of the population they serve (e.g., improving their health or tackling public health problems). These activities, therefore, do not constitute research with human subjects and thus are not subject to the ethical standards that govern research, such as prior approval by a REC. There is another normative framework aimed at ensuring that these public health activities adhere to ethical standards, such as *WHO Guidelines on Ethical Issues in Public Health Surveillance*¹.

It can be difficult to distinguish between research and other public health initiatives and activities, particularly during a health emergency. For this reason, the determination of whether an initiative constitutes research with human subjects should be made by an independent third party, such as a REC. Below are several resources that can help in distinguishing research from other public health activities.

- Centers for Disease Control and Prevention of the United States. CDC's Policy on distinguishing public health research and public health non research. Atlanta: CDC; 2010. Available from: <https://www.cdc.gov/os/integrity/docs/cdc-policy-distinguishing-public-health-research-nonresearch.pdf> (This policy includes examples that serve as a guide to distinguish between public health research and public health activities that do not have research purposes).
- Pan American Health Organization. Cash R, Wikler D, Saxena A, Capron A (eds.). Casebook on ethical issues on international health research. Washington, D.C: PAHO; 2014. Available from: <https://iris.paho.org/handle/10665.2/6082>.
- World Health Organization. Ethics in epidemics, emergencies and disasters: Research, surveillance and patient care. Training Manual. Geneva: WHO, 2015. Available from: <https://www.who.int/publications-detail-redirect/9789241549349>.
- Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, and the Social Sciences and Humanities Research Council of Canada. Tri-Council policy statement: Ethical conduct for research involving humans – TCPS2 2018. Ottawa: Canadian Institutes of Health Research; 2018. Available from: https://ethics.gc.ca/eng/policy-politique_tcps2-epc2_2018.html.
- Pan American Health Organization. When does research need ethics review? [YouTube]. Washington, D.C.: PAHO; 2021. Available from: https://www.youtube.com/watch?v=3nT_2Gnnerg
- Pan American Health Organization. Infographic: When does research need ethics review? Washington, D.C: PAHO; 2021. Available from: <https://www.paho.org/en/documents/infographic-when-does-research-need-ethics-review-0>

REC: Research ethics committee; WHO: World Health Organization; PAHO: Pan American Health Organization.

Note: ¹ World World Health Organization. WHO guidelines on ethical issues in public health surveillance. Geneva: WHO; 2017. Available from: <https://www.who.int/publications/i/item/who-guidelines-on-ethical-issues-in-public-health-surveillance>

Some research ethics topics that are pressing in health emergencies continued to pose challenges, such as community engagement and certain aspects of informed consent processes, e.g., to facilitate the use of samples and data for future studies. Other topics required specific ethics guidance, such as human challenge trials, which were reconsidered in the Zika outbreak (17, 18). Finally, there was widespread unfamiliarity with alternative research designs, such as adaptive designs, (19) which have great potential in emergency situations (20).

As soon as the COVID-19 pandemic started, and in response to the urgency of conducting research to understand the virus and find safe and effective interventions to identify, prevent, treat, and guide the public health response, PAHO published guidance aimed at catalyzing ethical research (2, 3, 4, 5, 6, 7) and worked closely with national authorities and RECs to implement these guidelines. The initial priority was to issue detailed guidance to ensure that RECs' ethics review and monitoring processes were agile yet rigorous (3, 4). The implementation of these guidelines was rapid, as table 1 illustrates.

Table 1. Guidance and regulations issued to accelerate the ethics review of COVID-19 research, by country and issuing authority.

Country	Guidance and regulations	Issuing authority
Argentina	Resolution No. 908/2020, Ethical and operational guidelines for the accelerated ethics review of research involving human beings related to COVID-19 (12 May 2020).	Ministry of Health.
	Measures and recommendations for clinical pharmacology studies during the COVID-19 pandemic (20 March 2020).	National Administration of Drugs, Food and Medical Technology (ANMAT by its Spanish acronym).
Brazil	Guidance for the conduct of research and RECs activities during the pandemic caused by the SARS-CoV-2 (COVID-19) (9 May 2020).	National Research Ethics Commission (CONEP by its Portuguese acronym).
	Technical Note No. 23/2020/SEI/COPEC/GGMED/DIRE2/ANVISA (28 July 2020).	National Sanitary Surveillance Agency (ANVISA by its Portuguese acronym).
Chile	Recommendations of the Ministerial Health Research Ethics Commission for the scientific ethics committees for the review of research protocols in the context of the COVID-19 pandemic (3 June 2020).	Ministerial Health Research Ethics Commission (CMEIS by its Spanish acronym).
	Recommendations of the Consultant Ad hoc Scientific Ethics Committee for Scientific Research concerning COVID-19 Vaccines of the Ministry of Health (December 2020).	Consultant Ad hoc Scientific Ethics Committee for Scientific Research concerning COVID-19 Vaccines of the Ministry of Health.
Colombia	External circular 1000-174-20 (July 2020).	National Institute for Drugs and Food Surveillance (INVIMA by its Spanish acronym).
Costa Rica	Announcement 1: Specific considerations for biomedical research in the framework of the COVID-19 pandemic (April 2020).	National Health Research Council (CONIS by its Spanish acronym).
	Announcement 2: Recommendations for the conduct of biomedical research during the COVID-19 health emergency in Costa Rica (August 2020).	
	Procedure Manual to streamline the ethics review and ethical scientific oversight of biomedical studies related to COVID-19 (17 July 2020).	Costa Rican Social Security Administration.
Dominican Republic	Announcement: CONABIOS during COVID-19 (April 2020).	National Bioethics in Research Council (CONABIOS by its Spanish acronym).

Country	Guidance and regulations	Issuing authority
Ecuador	<p>Ministerial Agreement No. 0003: Regulation for the development of health research conducted during the health emergency (16 April 2020). <i>Repealed.</i></p> <p>Ministerial Agreement No. 00104: Regulation for the approval and development of health research related to COVID-19 (December 2020).</p>	Ministry of Public Health.
Mexico	<p>Statement, Bioethics during the COVID-19 pandemic (12 March 2020).</p> <p>Announcement No. 007 COVID-19, Functioning of the RECs during the health emergency and extension of the suspension of procedures (4 May 2020).</p> <p>Extraordinary measures related to clinical studies during the COVID-19 pandemic (21 April 2020).</p>	<p>National Commission on Bioethics (CONBIOÉTICA by its Spanish acronym).</p> <p>Federal Commission for Protection against Sanitary Risks (COFEPRIS by its Spanish acronym).</p>
Panama	<p>Resolution No. 373 that establishes the rapid administrative procedure for the registry and oversight of research related to health emergency situations, disasters, or outbreaks of diseases and designates the National Committee on Bioethics in Research to manage the ethics review of these protocols (13 April 2020). <i>Repealed.</i></p> <p>Resolution No. 400 by which the special procedure to register and oversee research protocols related to health emergency situations, disasters, or outbreaks of diseases is regulated, and designates the National Committee on Bioethics in Research to manage the ethics review of these protocols (7 June 2021).</p> <p>PO-26, Operating procedures for the streamlined review of research protocols in response to health emergencies, disasters, or disease outbreaks, version 1.3 (June 2021).</p>	<p>Ministry of Health.</p> <p>National Committee on Bioethics in Research (CNBI by its Spanish acronym).</p>

Country	Guidance and regulations	Issuing authority
Peru	<p>Supreme Decree No. 014-2020-SA which establishes measures to ensure the adequate conduct of clinical trials for COVID-19 in the country (11 April 2020).</p> <p>Chief Resolution No. 096-2020-J-OPE/INS which establishes the National Transitory Research Ethics Committee for the ethics review and oversight of clinical trials of COVID-19 disease (13 April 2020).</p> <p>Chief Resolution No. 097-2020-J-OPE/INS which approves the procedure for the ethics review of clinical trials related to COVID-19 disease (13 April 2020).</p> <p>Directorial Resolution No. 120-2020-OGITT/INS which approves the operating procedures of the National Transitory Research Ethics committee for the ethics review and oversight of clinical trials of COVID-19 disease (13 April 2020).</p> <p>Chief Resolution No. 139-2020-J-OPE/INS which approves the technical document: Guidelines for the conduct of clinical trials during the COVID-19 pandemic (26 June 2020).</p>	<p>Ministry of Health.</p> <p>National Institute of Health (INS by its Spanish acronym).</p>

REC: Research ethics committee

Source: Adapted from Palmero A, Carracedo S, Cabrera N, Bianchini A. Governance frameworks for COVID-19 research ethics review and oversight in Latin America: An exploratory study. BMC Med Ethics. 2021;22(147). Available from: <https://bmcomedethics.biomedcentral.com/articles/10.1186/s12910-021-00715-2>

Consequently, research was conducted very quickly. Less than six months after the pandemic was declared, 285 of the 5213 entries registered in the WHO International Clinical Trial Registry Platform (ICTRP) pertained to Latin America and the Caribbean, and 202 were described as *interventional studies*. 170 out of those 202 were clinical trials on products to treat or prevent COVID-19 and 75% were conducted in Brazil, Mexico and Argentina – in this order (21) (table 2 and box 3).

Table 2. Clinical trials from Latin America and the Caribbean countries registered in the International Clinical Trials Registry Platform, 19 August 2020

Country	No.
Brazil	71
Mexico	52
Argentina	24
Colombia	15
Cuba	12
Peru	12
Chile	9
Puerto Rico	3
Ecuador	2
Honduras	1
Dominican Republic	1
TOTAL	202

Source: Carracedo S, Palmero A, Neil M, Hasan-Granier A, Saenz C y Reveiz L. The landscape of COVID-19 clinical trials in Latin America and the Caribbean: Assessment and challenges. Rev Panam Salud Publica. 2021;45:e33. Available from: <https://iris.paho.org/handle/10665.2/53150>

Box 3. Characteristics of clinical trials on interventions to prevent or treat COVID-19 from Latin America and the Caribbean registered in the International Clinical Trials Registry Platform, 19 August 2020

Characteristics (total: 170 trials)

- 141 (45%) were randomized clinical trials.
 - 77 had a control group and were at least partially blinded.
- 104 (61%) had a sample size of 200 or fewer individuals.
 - The smallest sample size was 9 individuals.
- The most frequently studied interventions were convalescent plasma, hydroxychloroquine/chloroquine (HCQ/CQ) and azithromycin (in that order).
 - 27 single-site clinical trials on convalescent plasma, the majority of them with sample sizes of less than 100 participants.
 - In Mexico, seven plasma trials included 281 participants.
 - 14 out of 26 studies of HCQ/CQ were conducted in Brazil.
- 18% were multinational trials, and in all cases, they involved a collaboration with a country outside of Latin America and the Caribbean.
 - None of them involved collaboration between countries of Latin America and the Caribbean.
- 78% of the clinical trials conducted within a single country did not have a commercial sponsor.

Note: The clinical trials presented here are from the following countries (ordered by the number of clinical trials registered, from highest to lowest): Brazil, Mexico, Argentina, Colombia, Cuba, Peru, Chile, Puerto Rico, Ecuador, Honduras and Dominican Republic.

Source: Carracedo S, Palmero A, Neil M, Hasan-Granier A, Saenz C y Reveiz L. The landscape of COVID-19 clinical trials in Latin America and the Caribbean: Assessment and challenges. Rev Panam Salud Publica. 2021;45:e33. Available from: <https://iris.paho.org/handle/10665.2/53150>

By conducting a high number of studies and, specifically, clinical trials, the Region has responded rapidly to the COVID-19 pandemic, which is highly positive (22, 23). However, the trend towards small, repetitive trials, and studies that are not designed to produce meaningful conclusions about the safety and efficacy of the interventions is still a major challenge (21). It is thus urgent to learn from this experience to ensure that, in a future health emergency, research conducted in the Region has high social and scientific value and is capable of answering research questions quickly in order to guide the emergency response. This entails strengthening local research capacities and establishing mechanisms to coordinate and collaborate in the development of randomized clinical trials within the same country, at the subregional level, and as part of regional and global research initiatives (21, 22, 23).

Moreover, a rapid response in research ethics does not imply lack of challenges. On the contrary, challenges have been shared and discussed with health authorities, RECs, and researchers from different countries of the Region in a series of regional dialogues (Table 1). Some challenges were caused by the measures initially taken to contain the spread of the virus, which impacted the processes for ethics oversight and further impeded ordinary processes to obtain the consent of research participants, which as a rule are in-person, use paper forms, and require participants' signatures. The COVID-19 pandemic has highlighted the need to rethink classic informed consent processes and to adopt alternative ones (e.g., virtual, electronic, or audiovisual systems) that adjust to the constraints of the emergency without compromising the guarantee of voluntary participation in research (Table 3).

Table 3. Examples of countries that adopted alternative informed consent processes for participation in research during the COVID-19 pandemic

Argentina	Established that customary mechanisms for obtaining consent may not be adequate and allowed the adoption of alternative processes, which must be justified and registered in the medical record (Resolution No. 908/2020, Ethical and operational guidelines for accelerated ethics review of research involving human beings related to COVID-19 [12 May 2020]).
Brazil	Allowed alternatives to usual informed consent processes, which could be carried out through digital tools or electronic platforms (Guidance for the conduct of research and RECs activities during the pandemic caused by SARS-COV-2, COVID-19 [9 May 2020]).
Peru	Established that the informed consent processes be conducted using digital tools (phone call, email) and orally, in presence of a witness (Chief Resolution No. 139-2020-J-OPE/INS, Guidelines for the conduct of clinical trials during the COVID-19 pandemic [26 June 2020]).

REC: Research ethics committee

The duration of the pandemic has also posed numerous unforeseen challenges that have led, for example, to modifying strategies for the ethics oversight of research throughout the pandemic (chapter 3). Other challenges pertain to the fragility of research ethics systems and the continuing need to strengthen research ethics capacities, particularly in topics that are prominent in health emergencies, such as human challenge trials for which, during the pandemic, WHO produced general ethics guidance (24) and guidance specific to COVID-19 (25).

This publication builds on the regional experience that led to revising and supplementing PAHO's ethics guidance for COVID-19. Its goal is to consolidate ongoing learning processes and facilitate the implementation of guidance to catalyze ethical research in future emergencies caused by epidemics, outbreaks or natural disasters.

CHAPTER 2.

HOW CAN TRUST IN RESEARCH CONDUCTED IN EMERGENCIES BE STRENGTHENED? TRANSPARENCY AND PUBLIC ENGAGEMENT

Catalyzing ethical research in emergencies entails responsibilities for health authorities, researchers, research institutions, and RECs. However, conducting research does not fall exclusively on these stakeholders. Research is only possible if there are people willing to participate in studies, and communities willing to host them. Without this generous contribution to the production of knowledge, it would not be feasible to conduct research, especially during emergencies, where rapid and concerted action is required.

Research aims ultimately at benefiting populations by understanding better the pathogen in question in order to guide the public health response, and discovering safe and effective interventions for its identification, prevention and treatment. However, the COVID-19 pandemic has highlighted that this benefit, which presumes the successful implementation of research results, is only fully achieved if there is trust in research and in the authorities who oversee it and act in response to those results.

Indeed, the pandemic has helped to bring research closer to the population: research is no longer a topic discussed only among experts. Research has received media coverage and is part of social conversations. However, the pandemic has also highlighted some of the challenges that Latin America and the Caribbean were facing before the coronavirus, such as a lack of public information on the conduct of health research, the benefits that result from it, and the safeguards needed to conduct research ethically. Moreover, in certain realms there is a negative perception of research with human participants and a resulting distrust in research and in many entities that conduct it or oversee it.

It is difficult to conduct research in this scenario, especially in health emergencies that pose the additional challenge of maintaining public trust in research ([1](#)). This has been particularly problematic during the COVID-19 pandemic: the proliferation of false information that has circulated online and on social media has undermined trust and added the task of correcting this information with truthful data that is easy for the general public to understand.

Transparency is a key component of the ethical governance of research that, in health emergencies, is essential to promote public trust in research and the public health response. Indeed, the pandemic revealed the urgent need to act to strengthen research transparency. If society and all stakeholders know what research is being conducted and what mechanisms are in place to ensure that research is conducted ethically, they will be more willing to contribute to research efforts and trust in their results, and to demand that all aspects of the response be supported by scientific evidence. Populations should also be continuously informed about the importance of conducting research during the emergency and, if an unproven intervention is offered outside of a research protocol during the emergency, it must be clearly communicated that this is not research and that the relevant ethics guidance for this scenario should be followed (chapter 5).

Box 4. Examples of initiatives by national authorities to strengthen transparent communication about ongoing research during the COVID-19 pandemic

Argentina: The National Administration of Drugs, Food and Medical Technology (ANMAT by its Spanish acronym) publishes on its website the COVID-19 clinical trials as they are authorized. See: <https://www.argentina.gob.ar/anmat/regulados/investigaciones-clinicas-farmacologicas/Estudios-autorizados-COVID19>. The Ministry of Health created a COVID-19 research observatory with the goal of maintaining an updated registry of the studies that were approved by the country's RECs. It can be consulted here: <https://www.argentina.gob.ar/salud/investiga/investigaciones>.

Brazil: The National Research Ethics Commission (CONEP by its Portuguese acronym) created the Brazil Platform Observatory, which was conceived before the pandemic but initiated with the registry of COVID-19 research with human subjects. For more information, go to: <https://observatoriopb.cienciasus.gov.br/>

Colombia: The National Institute for Drugs and Food Surveillance (INVIMA by its Spanish acronym) created a site on its website to inform about COVID-19 clinical trials. Although the site is currently disabled, information on approved clinical trials is available at: https://app.invima.gov.co/oficina_virtual/knowledgebase.php?article=14

Peru: In addition to requiring the registry of all clinical trials (including those on COVID-19) in the Peruvian Registry of Clinical Trials (REPEC by its Spanish acronym), which forms part of ICTRP, the National Institute of Health (INS by its Spanish acronym) started to require the registry of other COVID-19 studies in the Registry of Health Research Projects (PRISA by its Spanish acronym). See: <https://repec.ins.gob.pe> and <https://prisa.ins.gob.pe>, respectively.

REC: Research ethics committee; ICTRP: International Clinical Trials Registry Platform

Systematic and proactive action is necessary to ensure transparency of information regarding research studies and their progress. Yet trust in research also requires appropriate engagement of the communities that hosted the studies along with fair treatment of them and research participants. Moreover, even before research begins, the community should be engaged to ensure that the study is responsive to local needs and priorities and that its design is acceptable to the population that will host it. This engagement is key during emergencies because it ensures the social value of research and promotes trust in the resulting interventions. To the extent that health emergencies impact society as a whole, engagement should be at this level and not only at the level of specific communities (as is the case, for example, when a study is only of interest to those affected by a particular disease). Public engagement also facilitates consent processes that tend to be more difficult during emergencies (26).

Throughout the conduct of research, and after its conclusion, research participants and the communities that hosted the study should be treated respectfully and fairly. They should be informed about the study results and ensure that they receive what was deemed fair when initiating the study; for example, access within a reasonable timeframe to the intervention that resulted from the study to which they contributed. If research participants and their communities are not treated respectfully and fairly, it will be impossible to sustain trust in research.

In sum, it is imperative to take action to strengthen trust in research and in the interventions that research proves safe and effective. Building trust in research is a fundamental component of ethics preparedness for emergencies, and a crucial aspect of the ethical governance of research. To achieve this, the different stakeholders must take various measures that are not limited to health emergency scenarios.

2.1. Actions for national authorities

1. Ensure the registration of all research with human participants that has been approved to take place in the country so the information about the research studies is publicly available and easily accessible to the population.
 - a. Require the registration of clinical trials in a WHO-accredited registry, i.e., one that feeds ICTRP (27), before enrolling participants.
 - This requirement should apply to all clinical trials, defined as all studies in which participants are prospectively assigned to a health-related intervention, and not only those studying drugs and medical devices. The inclusion of all clinical trials in ICTRP ensures that their information is public and that they are identifiable with a single search at the global level. Countries do not need to have their own WHO-accredited registry to ensure that all trials taking place in the country appear in ICTRP. It is sufficient to require (e.g., through a ministerial resolution) the registration of trials in any registry that is part of ICTRP and allows the registration of clinical trials from other countries (e.g., in the Region of the Americas, [ClinicalTrials.gov](https://www.clinicaltrials.gov))
 - RECs and regulatory authorities overseeing clinical trials should require researchers to provide the registry information of the trial before enrolling the first participant and to include it in the informed consent documents of the study.
 - In adherence to WHO standards, researchers should also be required to add the trials results to the registry as soon as they are available (28).
 - b. Make available to the public a list with the basic information of the studies with human participants undertaken in the country.
 - The website of the relevant health authority should include a list of all studies with human subjects that are being conducted in the country. While this is advisable in general, it is reasonable to prioritize studies with human participants that are related to the health emergency. For clinical trials, the ICTRP code of the trial or the hyperlink to the registry entry should be included on the website.
 - RECs can be required to periodically provide to the oversight authority a list of the studies they have approved, in order to populate this site and keep the information up-to-date.
 - c. Require the registration of unproven interventions that are exceptionally offered outside of research during the emergency in a different registry that distinguishes them from interventions offered as part of research. This information should be available to the public; for example, published on the website of the relevant health authority and shared through other appropriate channels to provide information to the public during the health emergency (chapter 5).
2. Keep the records about the studies that RECs have reviewed and not approved and share it, as needed, with other RECs that are asked to review the same protocol.
 - a. Establish mechanisms to periodically gather from RECs the information about the studies that have been reviewed and not approved, and to share it (with the corresponding decision) with other RECs that request it.
3. Inform society about how research is conducted and the mechanisms to ensure it is ethical.

- a. Establish communication strategies to inform the public, through different channels (social media, web sites, announcements in public spaces, etc.), about the importance of conducting research when responding to emergencies, how research is conducted, and the safeguards to ensure the protection and ethical treatment of participants throughout the study, which include ethics oversight by RECs. For this purpose, authorities can use and adapt communication resources developed by PAHO (table 4). It is also important to create communication channels for the population to seek and obtain clarification about research and its ethical governance.

Table 4. Communication resources developed by the Pan American Health Organization during the COVID-19 pandemic

Short videos	<ul style="list-style-type: none"> • Why is fighting COVID-19 a group effort? [YouTube]. Washington, D.C.: PAHO; 2021. Available from: https://www.youtube.com/watch?v=5-8v826Rk1c • What is needed to fight COVID-19? [YouTube]. Washington, D.C.: PAHO; 2021. Available from: https://www.youtube.com/watch?v=O11acaLa8_Y • Why do scientists change their views? [YouTube]. Washington, D.C.: PAHO; 2021. Available from: https://www.youtube.com/watch?v=xZKnbsdSBNU • Why should we get a COVID-19 vaccine? [YouTube]. Washington, D.C.: PAHO; 2021. Available from: https://www.youtube.com/watch?v=uxcb9s0dpJg • When does health research need ethics review? [YouTube]. Washington, D.C.: PAHO; 2021. Available from: https://www.youtube.com/watch?v=3nT_2Gnnerg • What do research ethics committees review? [YouTube]. Washington, D.C.: PAHO; 2021. Available from: https://www.youtube.com/watch?v=Xd2cntkhllQ
Social media cards	<ul style="list-style-type: none"> • Ethics and research. Washington, D.C.: PAHO; 2020. Available from: https://who.canto.global/s/QFV49?viewIndex=0&from=curatedView&display=curatedView • Research with children. Washington, D.C.: PAHO; 2021. Available from: https://www.paho.org/en/documents/social-media-cards-research-children-0
Infographics	<ul style="list-style-type: none"> • Ethics and research - 10 key points about research during the pandemic. Washington, D.C.: PAHO; 2020. Available from: https://www.paho.org/en/documents/infographic-ethics-research-10-key-points-about-research-during-pandemic • Why should we include children in health research? Washington, D.C.: PAHO; 2021. Available from: https://www.paho.org/en/documents/infographic-why-should-we-include-children-health-research • When does research need ethics review? Washington, D.C.: PAHO; 2021. Available from: https://www.paho.org/en/documents/infographic-when-does-research-need-ethics-review-0 • What does a research ethics committee review? Washington, D.C.: PAHO; 2021. Available from: https://www.paho.org/en/documents/infographic-what-does-research-ethics-committee-review-0

2.2. Actions for researchers

1. Include as part of research protocols a public engagement plan, from the planning stages and throughout the study, with an adequate budget to carry it out. To engage the public, research teams should establish transparent and sustainable bidirectional communication channels between the public (including the potential research participants) and the researchers, and use approaches that are appropriate for emergency settings, such as meetings and forums on virtual platforms and social media. The plan should also ensure that research results are shared with research participants using friendly language.

2. Follow up studies rigorously. This entails keeping up to date with evidence that may emerge during the emergency and impact ongoing research. Researchers should maintain continuous communication with RECs in case modifications are needed to ensure studies remain ethical (chapter 4).
3. Share research results rapidly in order to guide decision-making (29, 30). Researchers (including those working at government institutions) have the duty to make their research results publicly available without delays. This entails promptly sharing research results with the health authority, including all relevant information, publishing them in open access journals, and adding them to the registries that feed ICTRP (28). Researchers should also promote other research, which implies sharing data and samples with other researchers to the extent that it is possible to do so ethically (chapter 6).

2.3. Actions for research ethics committees

1. Make publicly available a list of the studies related to the health emergency that were reviewed and their respective decisions (whether approved or not), as well as the list of unproven interventions offered outside of research that have been reviewed (chapter 5).
2. Inform the public (e.g., through web pages or social media) about the purpose of RECs and their role during health emergencies, and communicate, as needed, about the ethical aspects of research with human participants that could be challenging in emergencies or perceived as problematic (e.g., why the use of a placebo may be acceptable in a study if a product has been already authorized or when participants could have access to the interventions being studied) or if complications arise during the conduct of research.

2.4. Actions for research funding institutions

1. Require that all funded clinical trials be prospectively included in a registry that feeds ICTRP, and their results added in the corresponding registry in a timely manner.
2. Encourage those who receive research funding to publish a list of the studies with human participants that they are conducting, e.g., on the institution's website or through other mechanisms established by the health authority.
3. Require the prompt publication of the results of funded research in open access journals.

CHAPTER 3.

HOW TO ENSURE THAT THE ETHICS REVIEW AND MONITORING OF RESEARCH CONDUCTED BY RESEARCH ETHICS COMMITTEES ARE AGILE YET RIGOROUS IN EMERGENCIES

In health emergencies as well as in normal circumstances, every research project with human participants must be submitted to a REC for review and obtain approval before the study begins. Research with human subjects conducted in response to an emergency must adhere to usual ethical standards and take into account additional precautions that may be relevant due to the emergency (1). In order to be able to rapidly conduct ethical research that is urgent in health emergencies, RECs should conduct accelerated ethics reviews without compromising their rigor. It is therefore necessary to adapt and seek alternatives to ordinary processes of ethics oversight, which include the review and monitoring of research (box 5).

Box 5. Ethics oversight conducted by research ethics committees

1. **Ethics review** of research projects with human participants before the projects begin.
2. **Monitoring** of approved research throughout the course of the study (also called *oversight*, in a more specific sense)

Adapting ethics review and monitoring of RECs to emergency contexts requires, first, avoiding multiple and repetitive review processes by various RECs and, second, ensuring that each ethics review process is agile, rapid, and rigorous. To avoid repetitive review processes, the relevant authorities should define in advance the strategy (or combination of strategies) for organizing the ethics oversight of all research involving human subjects that is best suited to their context. Regardless which strategy is chosen, RECs involved in the ethics oversight of emergency-related studies must in turn adopt rapid and adequately flexible procedures so that reviews and subsequent monitoring are, in fact, carried out rapidly and rigorously.

3.1. Organizational strategies

The first task of the relevant authorities is to define the organizational strategy for research ethics review and monitoring that best suits their context. To take rapid action at the outset of an emergency, the strategy must be defined in advance and formalized through the corresponding legal instruments, along with the necessary precautions to implement it efficiently and sustainably (e.g., allocating the necessary financial and human resources).

There is no single formula for the ethics oversight of research in emergencies. Possible strategies have been identified and are presented without an order of preference (table 5). The scope of each strategy can vary: it can apply to all emergency-related research with human subjects or only to a subset of such research that has been previously identified (e.g., multicenter studies or clinical trials). A mixed organizational scheme, involving more than one strategy, can also be adopted. Furthermore, it should be kept in mind that the duration of a health emergency can vary significantly (from weeks to years) and that, in general, a large volume of research is expected in emergencies, which in turn implies a large workload for the RECs designated for ethics oversight. Therefore, to ensure that the selected strategy is sustainable along with continuous agility in the ethics oversight, it is reasonable to consider combining strategies based on the duration of the emergency and the volume of work undertaken by RECs.

Table 5. Possible organizational strategies for ethics oversight of research in emergencies and examples of their use during the COVID-19 pandemic

	Strategy	Example
<i>Ad hoc</i> committee	A REC is created to conduct the ethics review and monitoring of emergency-related research with human participants for the duration of the emergency.	Peru created the National Transitory Research Ethics Committee for the ethics review and oversight of clinical trials on COVID-19 disease. It comprises members of RECs accredited by the National Institute of Health and is responsible for the oversight of all clinical trials with pharmaceutical products and medical devices for the prevention, diagnosis, and treatment of COVID-19 conducted during the health emergency.
National-level committee	A national-level REC or a REC of a national government entity is given the responsibility for the ethics review and monitoring of emergency-related research with human participants for the duration of the emergency.	At the beginning of the pandemic, Brazil's National Research Ethics Commission (CONEP by its Portuguese acronym) was designated as the national entity in charge of the ethics oversight of research related to COVID-19. However, given the considerable increase in protocols submitted for review, CONEP limited its scope to a subset of COVID-19 research (clinical trials and mental health research, among others) and established that the rest of the studies should be submitted to the corresponding REC as a matter of urgency. In Panama, research protocols addressing health emergencies, disasters, and disease outbreaks must be submitted to the National Committee on Bioethics in Research (CNBI by its Spanish acronym) for ethics oversight. However, during the COVID-19 pandemic, CNBI operating procedures were modified to delegate to seven institutional RECs the oversight of COVID-19 research that is not considered of high risk (observational studies or experimental studies that do not involve the development of new therapeutic interventions or commercial products).

	Strategy	Example
Extra-territorial committee	Various states (e.g., from a region or subregion) establish a REC or delegate to an existing REC the responsibility for ethics review and monitoring of emergency-related research with human participants to be conducted in their countries or territories, for the duration of the emergency.	
Provincial or sub-national committee	Depending on the country's governmental structure, a newly established REC or an existing REC, at each subnational level, is tasked with the ethics review and monitoring of emergency-related research with human participants to be conducted at that level for the duration of the emergency.	
Institutional committees	One or more institutional REC are tasked with the ethics review and monitoring of emergency-related research with human participants to be conducted in the country for the duration of the emergency. The selection of one committee or another may be based on various criteria, including, for example, the REC's experience, its operational capacity, its affiliation with a health institution with a large number of affected patients, the research topic, and the risks involved in the studies, among other criteria. It can also be decided that existing institutional RECs in the country are responsible for the ethics review and monitoring of emergency-related research with human beings, as in normal situations.	In Argentina, ethics oversight remained organized at the institutional level during the pandemic, and the health authority issued recommendations for the RECs to establish operating procedures that ensure rapid and rigorous ethics review of COVID-19-related research.

REC: Research ethics committee

It should be noted that health emergencies are characterized by uncertainty and changing scenarios. Implementation of these organizational strategies thus requires sustained efforts from stakeholders, especially in the case of long-term emergencies such as the COVID-19 pandemic. Authorities should continuously evaluate the strategies they implemented and adjust them as needed to the circumstances and needs of a particular emergency. Brazil and Panama illustrate the adaptation of the organization of research ethics oversight to the evolving demands of the COVID-19 pandemic.

Opting for a strategy that involves more than one REC in the review of the same research protocols during the emergency may result in practical difficulties for the oversight of multicenter studies. For this reason, RECs should have coordinated procedures in place to streamline reviews, avoid

duplication of efforts, and not waste time or research opportunities. In these cases, it is recommended that RECs agree on a single committee whose review and decision on each protocol will be binding for the rest of the RECs. This can be accomplished by establishing the responsibilities of the REC tasked with the review (e.g., monitoring and communications). A measure adopted during the COVID-19 pandemic in some jurisdictions of Argentina (Buenos Aires and Buenos Aires City) with a high number of institutional RECs is a good case in point. Faced with the submission of multicenter clinical trials, the relevant authorities established processes to convene meetings involving all RECs that had to review the trials, with the goal of conducting a joint review and agreeing on the decisions. Finally, in health emergencies, the role of RECs in the emergency use of unproven interventions outside of research should be considered (chapter 5). It is important to establish a strategy that also defines which RECs will be responsible for the ethical oversight of the use of unproven interventions.

3.2. Operating procedures of research ethics committees

All the organizational strategies for ethics oversight of research in emergencies must consider rapid and flexible standard operating procedures (SOPs) that ensure a rapid and rigorous review of research and an agile and adequate monitoring of ongoing studies. It is important to highlight the need for SOPs to be flexible enough to adapt the functioning of the RECs to the demands posed by the health emergency, especially when emergencies continue for a long period of time.

The most relevant topics to be considered in the SOPs are listed below, divided into three sections. The first section (internal organization of the research ethics committee) presents the aspects related to the REC organization and structure that it needs in order to function efficiently during emergencies. The second section (ethics review process) presents the most important points to ensure rapid ethics review. Finally, the third section (ethics monitoring) includes general aspects related to the follow-up of studies conducted during an emergency.

Annex 1 presents a template of SOPs that RECs can utilize for health emergencies.

3.2.1. Internal organization of the research ethics committee

Composition of a REC in emergency situations. Health professionals with relevant knowledge related to the emergency must be included, and increasing the number of REC members should be considered. Members must be available to rapidly review protocols. To achieve this, it is advisable to identify committee members who can commit to meeting the deadlines and have the relevant knowledge and expertise before protocols are assigned for review. If the REC does not have members with the needed characteristics, it can convene national or international experts, who are not part of the REC, to serve as independent consultants or *ad hoc* external reviewers.

Selection and recruitment of independent consultants. It is advisable to identify experts (researchers, health professionals, social scientists, methodologists, ethicists, etc.) on issues related to the emergency response and confirm their availability ahead of time, so the REC can rely on their support for the review of specific studies, as necessary. The REC should identify and adequately manage any conflicts of interest that consultants may have, and adopt measures to safeguard the confidentiality of information. It is possible that committee members will not be available to conduct rapid reviews because they are involved with the emergency response or are affected by the disease. In such cases, consultants may be called upon to serve as *ad hoc* committee members, with full decision-making capacity.

Training of members. Members and consultants invited to serve as *ad hoc* members should have knowledge about ethics of research with human subjects, including the ethical issues raised by research in emergency situations.

The REC Secretariat. It is indispensable for the REC to have a Secretariat that provides permanent support and is resourced to ensure adequate functioning of the committee during emergencies. Given that the REC's management of information and communications will be virtual, the personnel in charge of the Secretariat must know how to use the relevant digital and electronic tools.

Mechanisms for communication and coordination. Procedures for efficient communication and coordination of activities among RECs and health authorities should be established. Ideally, the activities of RECs and health authorities, such as the National Regulatory Authority (NRA) responsible for authorizing clinical trials, should be conducted simultaneously (31).

Digital registry and documentation archive. All documentation should be registered and archived digitally. It is important that the platforms or programs that are used guarantee the confidentiality of the information.

3.2.2. Ethics review process

Communications and submission of electronic documentation. The use of digital tools such as email or text messaging facilitates and streamlines REC's communications with its members as well as with researchers, authorities, and other agents involved with the studies. These tools are adequate in scenarios in which restrictions of movement could be imposed on the population to manage the emergency, and their use should therefore be encouraged as long as confidentiality of information is guaranteed. Online platforms for the review of research protocols such as ProEthos (32) facilitate the work of the committee and significantly decrease the amount of time required to submit documentation. If the committee does not have an online system in place, it should request that all documents be submitted through other digital tools. Committee members and researchers should provide the REC with an email address and a mobile number as a channel of communication and commit to checking them regularly during the emergency. Likewise, the committee should have a unique email address to receive, handle and register documents and information.

Flexibility in the requirements for the submission of documents. The review of studies should not be delayed because of formalities (e.g., missing supplementary documents or signatures on documents). RECs should require researchers to address pending issues within a reasonable time frame, while the REC reviews the study.

Mechanisms to identify and prioritize research. Mechanisms should be in place to identify which submitted protocols are related to the health emergency and prioritize their review. The REC should also have criteria to prioritize among the emergency-related research protocols based on health needs and the objectives of the studies.

Virtual meetings. Meetings should be conducted virtually, through video or telephone calls, to avoid exposing committee members to the risk of infection and to facilitate meetings given the restrictions on movement that could be imposed in emergencies. Researchers can be asked to join the call or the virtual meeting if it is necessary to ask them questions. It is thus advisable to inform researchers ahead of time about the date and time of the meeting, so they can be available.

Staggered review and decision-making. It is possible that a majority of committee members will be overwhelmed with duties related to the response to the health emergency or affected by the disease,

which could complicate their participation in virtual meetings. In this case, and in order to not affect the necessary quorum, committees can make use of staggered deliberations and decision-making. For example, committee members can share their analysis through digital tools, and deliberate and make decisions later in the same way.

Reduced quorum. Given the exceptional nature of the emergency, a lower-than-normal quorum of members may be allowed. The number of committee members, and their experience and knowledge relevant to the review of the studies must be considered. If members cannot attend virtual meetings, they may be able to send their comments, questions, and reviews electronically and be counted for quorum.

Minutes. All actions and decisions of the committee should be recorded in minutes. These minutes can be prepared and shared through digital tools and approved or signed electronically. Once the emergency is over, minutes can be included in the official REC records.

Tight deadlines. Streamlined reviews are justified by the need to respond in a timely manner. It is therefore necessary to set tight deadlines for reviewing protocols, holding meetings, sending communications to researchers, receiving their responses, and issuing REC's final decisions. While the time it takes for the REC to issue a decision depends on various factors (complexity, level of development and technical rigor of the study, number of observations, response times of researchers, duration of the sessions, and others), deadlines such as the following should be met:

1. The research protocol must be sent to members for review within 24 hours from receipt.
2. Committee members should not take more than 72 hours to review the research protocol.
3. The meeting should be conducted as soon as members complete their review.
4. Communication to the researchers following committee review should occur as soon as possible after the meeting.
5. Researchers should respond to the committee within 48 hours.

It is important to consider that the deadlines established by the REC may be adjusted according to the context and the needs of the emergency.

Ethics oversight of the use of unproven interventions outside of research. Procedures should be considered for the oversight of unproven interventions offered outside of research in order to ensure they adhere to the ethics criteria established under the *monitored emergency use of unregistered and experimental interventions* (MEURI) (chapter 5).

3.2.3. Ethics monitoring

As in ordinary circumstances, RECs have the obligation to monitor studies from start to finish, since their ethical acceptability may change as they are being implemented. During health emergencies, research monitoring can be staggered or carried out remotely in order to avoid subjecting committee members to risk, or affecting patient care or the operation of health care delivery centers. Ethics monitoring also needs to be done more frequently in light of the rapid production of new scientific evidence (chapter 4).

CHAPTER 4.

HOW CAN THE ETHICAL ACCEPTABILITY OF RESEARCH BE ENSURED IN RESPONSE TO EMERGING EVIDENCE?

After conducting a rigorous analysis, RECs should approve research projects that adhere to ethical standards and monitor them until their conclusion, because their ethical acceptability can change. For example, a study can cease to have social value if the question it aims to answer has been answered by another study with high-quality evidence. A study can also cease to have a favorable risk/benefit ratio if the study intervention is found to be riskier than initially thought, or if an effective treatment has already been found for the condition being studied. A consent process could cease to be adequate because it does not inform potential participants about alternative treatments that are now available but were not available at the initiation of the study (1).

In emergency situations –where evidence is produced quickly to improve the response– research protocols that were initially ethically acceptable may soon cease to be so. New scientific evidence can impact the social and scientific value of the studies, their risk/benefit balance, and other aspects of their ethical acceptability. Therefore, REC oversight of ongoing research during emergencies poses additional challenges, and both committees and researchers are responsible for ensuring that research continues to be ethically acceptable in light of the most up-to-date available evidence (box 6). In this context, this chapter aims to guide the ethical analysis and procedures for the oversight of research in response to the rapid production of evidence during emergencies.

Box 6. The case of hydroxychloroquine

During the initial phase of the pandemic, many studies tested hydroxychloroquine as a possible treatment for COVID-19. The RECOVERY (*Randomised evaluation of therapeutics for COVID-19*) clinical trial showed the futility of this drug as a treatment for patients hospitalized with COVID-19¹. Therefore, other ongoing studies had to be suspended or revised in order to analyze the possibility of modifying them. Among these, the *Solidarity* clinical trial of the World Health Organization proceeded to close the arm that studied hydroxychloroquine². This case illustrates how clinical trials that were ethically acceptable at the beginning of the pandemic ceased to be so on the basis of emerging new evidence.

Note: ¹ Oxford University. Randomised evaluation of COVID-19 therapy (RECOVERY). 2022. Available from: <https://www.recoverytrial.net/>.

² World Health Organization. COVID-19 Solidarity therapeutics trial. 2022. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments>

Research in response to emergencies should be monitored more often than usual because of the great speed at which new scientific evidence is produced in these scenarios. Researchers are responsible for continuously updating their knowledge related to the study and, especially, for reviewing the available scientific evidence at appropriate intervals. Importantly, decisions should

always be made on the basis of high-quality scientific evidence, which in turn depends on rigorous study designs, consistency of the results, precise confidence intervals, lack of bias, etc. (33). To update their knowledge, researchers can draw from the latest systematic reviews and meta-analyses of scientific evidence by entities such as Cochrane or other recognized institutions, such as PAHO and WHO, that synthesize evidence (34); and, in the case of COVID-19, by institutions that are part of the COVID-19 Evidence Network COVID-END (35). Researchers should discern the quality of the evidence they evaluate (33) and keep in mind that the value of available evidence can vary in a short time period. It should be also taken into account that there may be knowledge gaps in the evidence about subgroups or specific populations. Researchers are therefore advised to be attentive to the appearance of different types of publications related to their study (including preprints) and, preferably, make decisions based on studies published in peer-reviewed scientific journals (36). Finally, with the emergence of new scientific evidence that could affect the justification for a study or its conduct as established in the protocol, researchers should evaluate whether to continue, modify, suspend, or cancel the study, and rapidly inform the REC about their proposed course of action. RECs, in turn, should review the protocol, evaluate the measures proposed by researchers to guarantee that the study continues to adhere to ethical standards, and approve them if appropriate.

4.1. Operational recommendations for ethics monitoring

When first reviewing the protocol, the REC should ask researchers to justify their study on the basis of the most up-to-date available evidence. With the approval of the protocol, the REC should establish the manner and deadlines for the monitoring of the approved research according to the type of study and its level of risk. The monitoring plan should call for periodic reports, by established deadlines, for which researchers must justify the continuation of the study on the basis of newly available evidence, if any. If new evidence affects the conduct of the study, researchers should indicate the actions they will take.

Aside from the previously mentioned periodic presentation of reports, researchers should immediately inform the REC if at any moment they become aware of new evidence that could affect the development of the study and justify how they will proceed as a result. If the REC becomes aware of new evidence that puts the conduct of a study in question, it should ask researchers for a report justifying the way to proceed in response to this evidence.

The report on the newly available evidence that researchers present to the REC should include a summary of the most important points of their review and the references consulted. Based on this new evidence, researchers should justify whether they should continue, modify, suspend, or cancel the study (table 6).

Table 6. Possible monitoring actions in response to the reports of new evidence submitted by researchers

Action	Description
Continuation of the study	If researchers consider that a study can continue as initially planned, they should explain how it continues to have a favorable benefit balance regarding the risks, and how it continues to be ethical to conduct it without modification.
Modification of the study	If some of the elements of the study require modification (e.g., intervention arms or control, inclusion/exclusion criteria or the data being collected), researchers should justify these modifications and indicate the measures they will take to inform participants about these changes. The proposed modifications should be presented to the REC and undergo review quickly. It is important to bear in mind that modifications that are necessary because of an imminent danger to participant safety must be implemented immediately.
Suspension of the study	If researchers decide to suspend a study, e.g., to conduct a more exhaustive evaluation of the available evidence, they should justify their decision and indicate the measures they will take regarding participants: how they will inform them about the reasons for the decision and what will happen afterwards. After the pause, the study may continue without changes, require modifications, or be cancelled.
Cancellation of the study	If researchers decide to cancel the study, they should justify this decision and indicate the measures they will take regarding the participants: how they will inform them about the reasons for terminating the study, what will happen later, and what measures they will take to guarantee their security and wellbeing.

REC: Research ethics committee

The REC should evaluate the proposed course of action. To facilitate this analysis, both researchers and the REC can use the questions included in table 7 as a guide.

To assess the continuation or modification of a study, the REC should review the report that was presented and analyze whether it is pertinent to approve the study's continuation, approve the proposed modifications, request additional modifications, or suspend or cancel the study. Once the REC approves the modifications, researchers should take the necessary actions in a timely manner, for example, obtaining new consent from the participants if this was stipulated by the REC.

If the REC decides to modify, suspend, or cancel the study, researchers are responsible of communicating this decision immediately to the relevant health authorities. They should also record these changes as soon as possible in the respective research registries, including those that are part of ICTRP. In the case of the suspension or cancellation of the study, researchers should communicate this decision to the scientific community and the general public. The REC should also make public the suspension or cancellation of the study (e.g., by publishing the information on its web page) and inform the other involved institutions, RECs, or networks of RECs they belong to about this decision

Just as in ordinary situations, researchers should include in their community engagement plan strategies to communicate the new information about the study in a transparent way. In addition, amid the proliferation of information about new evidence in media and social media, the urgency of having agile mechanisms to keep participants and the general population continually informed is greater than ever. Information is key to mitigating concerns and clearing up misunderstandings that could reduce trust in research (chapter 2).

4.2. Ethical analysis when monitoring research

To justify continuing, modifying, suspending, or cancelling a study, an ethical analysis should be carried out in light of the new evidence. In normal circumstances, monitoring ongoing studies calls for ethical analysis. Yet the speed of the production of knowledge in health emergencies entails the need to do it more frequently. Below are some questions that illustrate this ethical analysis (table 7). These questions have been developed on the basis of an existing ethics review framework (37, 38, 39) and do not constitute a checklist, nor do they include all the questions a REC should consider when monitoring ongoing research protocols.

Table 7. Guiding questions for the ethical analysis of research monitored by committees, in response to new evidence

Theme	Questions
Social value	<ul style="list-style-type: none"> • Taking into account the newly available evidence, is it still valuable to carry out this study in this particular context? • What is the expected benefit of this study that is different from the benefits achieved by other similar studies that have been completed? • Has the research question already been answered (totally or partially)? If so, does this answer address the relevant endpoints for decision-making? • Should a change in the objectives of the study be considered?
Scientific value	<ul style="list-style-type: none"> • Taking into account the newly available evidence, is the methodological design still adequate to answer the research question? • Is the control mechanism in the study still appropriate in light of newly available evidence? • Taking into account the newly available evidence and the current context (e.g., the epidemiologic context), is it still feasible to carry out the study?
Fair participant selection	<ul style="list-style-type: none"> • On the basis of newly available evidence, should inclusion and exclusion criteria be modified to minimize risks for participants and maximize the potential benefits of the study? • To evaluate whether it is appropriate to modify the inclusion and exclusion criteria, it should be considered whether previous studies have demonstrated, for example, that the study intervention: <ul style="list-style-type: none"> – is risky for a subgroup, – is beneficial only for a subgroup, – is harmful for a subgroup.
Favorable risk/benefit ratio	<ul style="list-style-type: none"> • Taking into account the new evidence: is the risk-benefit balance still favorable? Are there new risks? Are these risks justified in light of the study's potential benefits? Does the study have the potential for greater or different benefits from those that were initially considered? • To evaluate whether the risk-benefit balance continues to be favorable, it should be considered whether previous studies have demonstrated, for example, that the study intervention: <ul style="list-style-type: none"> – is riskier than previously considered to be. – is harmful. – has no benefit. – has limited benefits. – has additional benefits than those previously considered. • Based on currently available evidence, should other measures be adopted to minimize risks or maximize the benefits of the study?

Theme	Questions
Informed consent	<ul style="list-style-type: none"> • Is there new information (e.g., regarding risks of the intervention under study) that could affect participants' decision to continue in the study? How will this information be provided to participants? • Has a modification of the protocol been identified, about which potential participants or those that are already enrolled in the study should be informed? • Is it necessary to reconstent participants?
Respect for participants	<ul style="list-style-type: none"> • During the conduct of the research, is there new evidence that participants should be informed about? • In light of newly available evidence, should additional or different measures be considered to monitor the wellbeing of participants throughout the study? • After having decided that the study should be suspended or cancelled, how should participants be informed? How will their safety and well-being be guaranteed? What medical care will they receive? How will it be ensured that they are covered for possible harms that may result from the study? • If an effective intervention is discovered in other studies, will this intervention be offered to participants in the study in question?

Furthermore, monitoring placebo-controlled clinical trials after drugs and other health technologies have been authorized for emergency use in health emergencies poses special challenges. In the absence of therapeutic alternatives, it is important to rigorously evaluate ethical issues related to access to these products by research participants and the justification for continuing studies to obtain more data on long-term safety and efficacy (e.g., on the immunity conferred by vaccines over time or on the impact of new virus variants on the effectiveness of drugs). On the one hand, the option of not unblinding the trial to provide the authorized intervention could negatively affect the population's perception of the research, as it could be considered an unfair decision; on the other hand, early termination of a study could invalidate its results and entail a waste of resources, efforts, and opportunities to generate knowledge (box 7).

Box 7. Questions that guide the monitoring of ongoing placebo-controlled clinical trials after an emergency use authorization of drugs and other health technologies has been granted

- Should the placebo-controlled arm continue? What is the benefit or scientific value of doing so? What are the implications of unblinding the study for the participants and the production of knowledge?
- Within the control group, who should be prioritized to receive the authorized intervention as soon as possible (e.g., health professionals or people in the highest risk categories)?
- What should be explained to participants?
- How can the continued participation of those not eligible to receive the authorized product now be promoted? Is participants' right to freely withdraw from the study being protected? What is the follow-up plan for people who decide to leave the trial?

Source: Adapted from World Health Organization. Emergency use designation of COVID-19 candidate vaccines: Ethical considerations for current and future COVID-19 placebo-controlled vaccines trials and trial unblinding. Policy brief. Geneva: WHO; 2020. Available from: https://apps.who.int/iris/bitstream/handle/10665/337940/WHO-2019-nCoV-Policy_Brief-EUD_placebo-controlled_vaccine_trials-2020.1-eng.pdf?sequence=1&isAllowed=y

CHAPTER 5.

HOW CAN THE ETHICAL USE OF UNPROVEN INTERVENTIONS OUTSIDE OF RESEARCH BE ENSURED IN HEALTH EMERGENCIES?

Rigorous research is necessary to prove the safety and efficacy of health interventions. When interventions are being tested – because it is not yet known whether they are safe or effective – safeguards are put in place to protect research participants. After the necessary studies have been completed, and interventions have been proven and established as safe and effective through rigorous processes led by a NRA, they are finally authorized and can be provided to patients to treat or prevent diseases. Since they are already proven (i.e., it is known that they are safe and effective) the safeguards required for research are no longer needed.

However, in health emergencies marked by high mortality, severe morbidity, and the absence of safe and effective treatments, it has been questioned if it is ethically acceptable to offer interventions that have not been previously proven as safe and effective outside the context of research. The ethical challenge is evident: when giving unproven interventions outside a research protocol, there are no safeguards in place to protect people receiving these interventions. Furthermore, knowledge about the safety and efficacy of these interventions, which is urgent in emergency settings, is not being produced.

PAHO and WHO recommend that unproven interventions be offered within research protocols, and specifically within randomized controlled trials capable of assessing safety and efficacy rapidly (31, 40, 41). However, there are some exceptional situations during health emergencies in which it could be ethically acceptable to use unproven interventions outside of research. For this scenario, there is a specific ethical framework with criteria aimed at ensuring the ethical use of these interventions. This framework was devised by WHO in response to the extraordinary challenges encountered during the 2014 Ebola outbreak, and was called *monitored emergency use of unregistered and experimental interventions* (MEURI) (12). MEURI aims at offering affected persons exceptional access to these interventions in view of their possible benefit, while ensuring that their use is monitored to protect people and contribute data to the generation of evidence. At the beginning of the COVID-19 pandemic, PAHO issued a guidance document that revised the MEURI framework by organizing the ethical considerations proposed by WHO into four core criteria for the ethical acceptability of the emergency use of unproven interventions outside of research (7). In 2022, WHO published general guidelines on the topic that adopt PAHO's four ethics criteria and recommendations (42).

5.1. Ethics guidance for the emergency use of unproven interventions outside of research: four ethics criteria

In a health emergency, if consideration is given to the use, outside of research, of an intervention whose safety and efficacy have not been previously proven for the condition in question, four relevant ethics criteria (table 8) must be followed. These ethics criteria establish whether it is ethically justifiable to proceed with the use of that intervention and, if so, how to proceed to ensure that this use is ethical. The ethics criteria pertain to the justification of offering such interventions outside the research setting, the ethical and regulatory oversight for this use, the consent process, and the contribution to the generation of evidence.

Table 8. Questions and ethics criteria for the use of unproven interventions outside the research setting

Question	Ethics criteria
Is the use of this intervention outside of research ethically justifiable?	1: Justification
If the use outside of research is justified, how should one proceed to ensure that this use is ethical?	2: Ethical and regulatory oversight 3: Informed consent process 4: Contribution to the generation of evidence

These criteria apply to all unproven interventions that are considered for use outside of a research setting in emergency situations, including preventive or therapeutic interventions; interventions of drugs, devices, or blood products; interventions previously authorized for a different condition and interventions that have not been proven safe and effective for any condition. The criteria have been conceived for health emergencies, so they do not aim to address situations that may constitute a clinical urgency that is not part of a public health emergency. Furthermore, as ethics criteria, it should be kept in mind that their correlation with existing regulatory nomenclatures (like *compassionate use* or *expanded use*, among others.) may be complex and, in certain jurisdictions, there may not be any regulatory category that corresponds to this use. The development or review of the relevant regulatory categories and processes should be done in light of these ethics criteria (9).

5.1.1. Justification

In emergency situations in which no proven effective treatment exists and it is not possible to initiate clinical studies – preferably randomized clinical trials – immediately, it *may be* ethically acceptable to offer to the population an unproven intervention outside the research setting if there is evidence that provides preliminary support for its safety and efficacy. An appropriately qualified scientific advisory body (such as a national or international scientific committee, PAHO or WHO) should evaluate the most up-to-date evidence on the basis of a rigorous assessment of the risks and potential benefits of the intervention. The use of the intervention can be justified only if it has been determined that the proposed intervention has a favorable risk-benefit profile.

This justification, however, will only be valid for a limited time period, i.e., until a research study can be initiated. Transition to a clinical trial should be sought as soon as possible to test as quickly as possible whether the intervention is safe and effective. Producing this knowledge is morally urgent in health emergencies, and the use of an intervention outside of research should not hinder the conduct of research.

5.1.2. Ethical and regulatory oversight

If it is determined that the use of an unproven intervention is justified in a health emergency, adequate ethical and regulatory oversight is necessary. This implies prior review and approval by a REC and the NRA, along with other relevant national authorities, in accordance with the local norms and the type of intervention.

This oversight entails guaranteeing the availability of resources to minimize the risks involved in the use of an unproven intervention outside of research. This includes ensuring that only products adhering to good manufacturing practices are used, and that other measures needed to minimize the risks of the intervention are in place (e.g., restricting the use of the intervention to populations for which there is a favorable risk-benefit profile).

Adequate ethical and regulatory oversight allows to corroborate adherence to the other ethics criteria, i.e., ensuring the use of the intervention is justified, the integrity of the consent processes, and the contribution to the generation of evidence. Careful oversight of the use of unproven interventions is key in scenarios of health emergencies, where evidence is volatile and knowledge is produced rapidly.

5.1.3. Informed consent process

Ethical emergency use of an unproven intervention outside of research entails that all persons receiving the intervention have provided prior consent. Informed consent is a process aimed at ensuring that people voluntarily decide, based on their own assessment of risks and benefits, whether or not they want to receive the intervention. As part of the process, people must be clearly informed that the intervention being offered has not been proven, so it might not benefit them and may even harm them. Also, people should be informed that they are not participating in a research protocol. As in other circumstances, proxy consent should be obtained as appropriate.

National health authorities have the responsibility of providing information about the risks and potential benefits of interventions that have not yet been proven safe or effective and ensure that these interventions are distinguished from those that have been already proven safe and effective. The mentioned authorities should further promote dialogue about unproven interventions offered outside of research with the goal of advancing clarity and avoiding false perception of benefits of the intervention. Public engagement is key for meaningful consent processes, particularly in the context of an emergency.

5.1.4. Contribution to the generation of evidence

Finally, for the emergency use of unproven interventions to be ethical, it must contribute to the generation of evidence. While this use is not part of a research study and aims at a *potential* benefit for those receiving the intervention, it must contribute to generating knowledge because the intervention is offered in the context of a health emergency characterized by the absence of proven therapeutic options.

The use of the intervention should therefore be monitored and the results of this monitoring should be documented and shared in a timely manner with the wider medical and scientific community. Health professionals responsible for the use of an unproven intervention have the obligation to collect the data that have been previously identified –in close coordination with the relevant national authorities– to provide information about the safety and efficacy of the intervention (box 8). This

data must then be shared without delay, accurately and transparently with all relevant national and global stakeholders.

For a systematic and efficient data collection and to avoid unduly burdening national authorities and RECs that are already overwhelmed in health emergencies, unproven interventions should be used as part of protocols or programs that offer access to a *group* of patients (rather than individual patients).

Box 8. Why should the use of unproven interventions outside of research be included in guidance for research?

Challenges in the Region of the Americas

The use of unproven interventions outside of a research setting has been one of the greatest ethical challenges during the COVID-19 pandemic in the Region of the Americas. This challenge can be explained by the lack of knowledge about the relevant framework for this scenario. WHO devised this framework in 2014 in response to the Ebola outbreak, but the Zika outbreak in the Region did not lead to discussions about the use of unproven interventions. Therefore, at the beginning of the COVID-19 pandemic there was no familiarity with the framework. Consequently, unproven interventions were used in the Region without adherence to the corresponding ethical standards and a considerable number of interventions were offered whose use was not justifiable on the basis of the available evidence due to an unfavorable risk-benefit profile. This has not only led to health harms but also diverted limited resources that could have been used for interventions that carry benefits for the population. Furthermore, widespread use of unproven interventions in some jurisdictions has generated the false perception among the population that the unproven interventions were beneficial, which in turn has made informed consent processes more difficult, undermined trust in health authorities, and hampered the conduct of clinical trials on these interventions.

The emergency use of unproven interventions outside of research should be included in research ethics guidance, since their use entails responsibilities for RECs and health authorities tasked with research oversight. Lack of clarity about oversight of emergency use of unproven interventions outside of research has led to erroneously characterizing interventions offered under the MEURI framework as *observational research*. This generates even more confusion because, by definition, these interventions do not constitute research. This practice further opens the door for characterizing interventions in a way that evades appropriate ethical and regulatory oversight, and erodes the public's trust in the health system's capacity to guarantee the ethical conduct of research.

A crucial lesson from the COVID-19 pandemic is that providing unproven interventions outside of research without adherence to the corresponding ethical standards negatively impacts research in general. While these are uses implemented *outside of a research setting*, to the extent that unproven interventions are as a rule only offered in research settings, it can be retrospectively concluded that this use constituted research conducted unethically, and that the research ethics system is not capable of ensuring the ethical conduct of research in health emergencies.^{1,2}

Therefore, RECs and health authorities responsible for research oversight should be knowledgeable about the MEURI ethical framework in order to ensure that, during health emergencies, unproven interventions are offered outside of research only if their use adheres to the appropriate ethics criteria.

REC: Research ethics committee; MEURI: Monitored emergency use of unregistered and experimental interventions; WHO: World Health Organization

Note: ¹ Sheridan MB. Mexico City gave ivermectin to thousands of covid patients. Officials face an ethics backlash. The Washington Post, 9 February 2022. Available from: <https://www.washingtonpost.com/world/2022/02/09/mexico-city-covid-ivermectin/>.

² Yang M. Arkansas jail's ivermectin experiments recall historical medical abuse of imprisoned minorities. The Guardian, 14 February 2022. Available from: <https://www.theguardian.com/us-news/2022/feb/14/arkansas-prison-covid-19-ivermectin-experiment-minorities-medical-abuse>.

5.2. Recommendations for the ethical use of unproven interventions outside of research in emergency situations

In emergency situations, the use of unproven interventions outside the research setting is ethical if it adheres to the four ethics criteria of the MEURI framework. The following general and operational recommendations aim at facilitating the adherence to these ethics criteria.

5.2.1. General recommendations

Exceptionality of the use of unproven interventions outside of research in emergency situations.

In health emergencies, unproven interventions should be used in the context of randomized controlled trials that make it possible to assess their safety and efficacy. Only in exceptional circumstances, in which unproven interventions cannot be offered in a research setting, they may be used ethically under the MEURI framework, which entails adherence to the four relevant ethics criteria. Interventions offered in accordance with the MEURI framework should not divert attention or resources from the clinical trials that need to be conducted and should not be extended beyond a limited timeframe because they should be transitioned to research as soon as possible.

Strengthening of ethical and regulatory oversight. Health authorities (NRAs or other relevant health authorities) and RECs should be empowered to use the MEURI framework and advance coordination to promote an adequate oversight in timeframes that are responsive to the health emergency (table 9).

Public engagement. Relevant health authorities should communicate to the population the importance of using interventions that are supported by scientific evidence, the need to evaluate interventions as part of research studies with adequate safeguards, and the risks of interventions that have not yet been scientifically proven. In the exceptional cases in which interventions under the MEURI framework are used, health authorities should clearly communicate that the interventions have not been proven, encouraging an open dialogue about their risks and potential benefits, and informing about the ongoing oversight.

Differentiated registration of unproven interventions offered outside of research in emergencies.

In order to ensure clarity about which unproven interventions are offered as part of research and which are offered under the MEURI framework during a health emergency, it is key that the latter be registered as well. All clinical trial registries –ICTRP, registries that feed ICTRP and other national registries that do not– should distinguish between protocols of clinical trials (or research in general) and those interventions offered under the MEURI framework.

5.2.2. Operational recommendations

Development of the protocol for the emergency use of an unproven intervention outside of research. The intervention must be proposed as part of a protocol that includes at least the following elements:

- background;
- scientific justification, based on the recommendations of a scientific committee;
- objectives;
- population to be offered the intervention;
- risks and potential benefits;
- measures to minimize risks;

- scientific data to be collected that may provide information on the intervention’s safety and efficacy;
- plan to offer the intervention;
- informed consent documents and details about the process;
- measures to protect confidentiality;
- data sharing plan; and
- proposal for the transition to research.

Box 9. Ethics oversight by the research ethics committee of unproven interventions offered outside of research in an emergency

What does a research ethics committee review?

The REC should evaluate whether the use of the proposed intervention adheres to the ethics criteria, i.e., justification, ethical and regulatory oversight, informed consent, and contribution to the generation of evidence. For this purpose, it should consider the following aspects:

- available scientific evidence justifies the intervention, based on its risk-benefit balance;
- the intervention is offered to the appropriate population;
- measures to minimize risks;
- informed consent process is adequate and in accordance with the emergency context. It specifies that the intervention has not been proven and explains what it consists of, along with its risks and potential benefits and the data that will be collected;
- data that will be collected are relevant to provide information about the safety and efficacy of the intervention;
- measures to safeguard the confidentiality of the data that have been taken;
- establishment of a procedure to rapidly share data with the health authorities, and the national and international scientific community; and
- proposed transition to offer the intervention as part of research.

What does a research ethics committee monitor?

Through reports from the health professional responsible for the intervention, the REC ensures that the intervention offered under the MEURI framework is still justified in light of newly available evidence. The analysis of the collected data or other studies may lead the REC to conclude that offering the intervention is no longer justifiable (e.g., because the risk-benefit profile is different from initial estimates, or because another safe and effective intervention is discovered). The REC may require modifications to the intervention or the way it is offered, or else its suspension or termination.

REC: Research ethics committee; MEURI: Monitored emergency use of unregistered and experimental interventions

Health authority involvement. The NRA and other relevant health authorities need to know which interventions are being offered in the country under the MEURI framework, as well as evaluating and authorizing them prior to their initiation. Health authorities are recommended to collaborate in developing the protocol for the intervention offered under the MEURI framework, in order to ensure the quality and usefulness of the data that will be collected. Additionally, health authorities should:

- maintain a record of the interventions offered under the MEURI framework in the country;
- determine the timeframe to reassess the scientific evidence justifying the use of the intervention under the MEURI framework;

- establish the mechanisms and procedures to present the data collected as part of a protocol offered under the MEURI framework;
- establish the mechanisms and procedures to oversee the intervention, which entails the possibility of requesting modifications, or suspending or terminating the intervention; and
- evaluate the proposal for the transition to research and verify that it is implemented.

Registry of the protocol offered under the MEURI framework. To ensure the transparency of interventions offered under this framework, interventions should be included in registries that feed ICTRP and in any other registry that may be locally required upon approval. If registries have not implemented mechanisms to distinguish interventions that are offered under the MEURI framework, the title of the protocol should state that it is not research, but rather an intervention offered under the MEURI framework.

Efficiency and coordination. For adequate ethical and regulatory oversight of interventions offered under the MEURI framework during health emergencies, health authorities and RECs must have rapid and efficient mechanisms for communication and coordination. As with research proposals, health authorities and RECs should proceed simultaneously and avoid duplicating efforts (e.g., many RECs reviewing the same protocol) (chapter 3). Additionally, health authorities, RECs, and health care professionals responsible for interventions offered under the MEURI framework should work closely from the beginning of their activities.

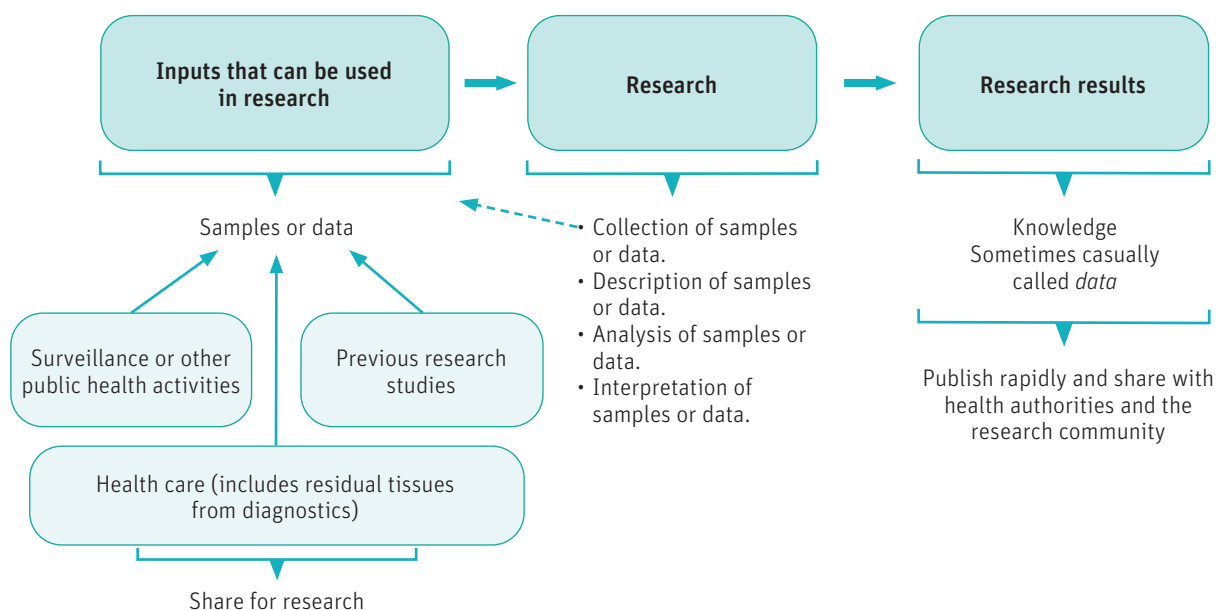
Monitoring the intervention. The REC and the NRA (or other relevant health authority) should monitor the intervention offered under the MEURI framework (box 9). The health care professional responsible for the intervention must reassess it periodically in the light of new evidence, and report to the REC and the NRA (or other relevant health authority) using the previously established timeframes and procedures.

CHAPTER 6.

HOW TO ENSURE THAT DATA AND SAMPLES ARE SHARED ETHICALLY FOR FUTURE RESEARCH

People’s biological samples and data may have great research potential because they can be critical for developing diagnostic measures, preventive or therapeutic interventions, or guiding public health through a better understanding of a pathogen. Samples and data with research potential do not only provide from research settings; they can also be collected in other scenarios, such as public health surveillance and health care delivery. Regardless of the collection scenario, it is ethically important to share data and samples for the conduct of future research, i.e., to facilitate research studies that are not planned at the time of collection but that may be conducted in the short or long term by local or international researchers (figure 1).

Figure 1. Role that samples and data can play in research



In health emergencies, it is important to encourage the collection of samples and data with a view to sharing them for future research. Some samples and data are only available during an emergency, so if they are not properly collected and stored at that time, the necessary inputs for future socially valuable research will not be available; e.g., once an outbreak is over, the pathogen is no longer circulating, so it will not be possible to collect certain samples. This happens with human biological samples as well as with other non-human samples, such as samples of viruses or other pathogens. Collecting samples and data to share them rapidly and efficiently in the future helps to accelerate research and improve the response to health emergencies. It also strengthens and promotes collaborations between research groups at the national, regional, and global levels.

However, sharing samples and data for research purposes poses challenges: How can we ensure that samples and data are collected, stored, and shared ethically? How can samples and data be shared fairly, especially in global collaborations, so that people and populations who contributed to research by providing their samples and data benefit from future studies? These challenges may be more pressing in Latin America and the Caribbean because of the lack of relevant regulatory frameworks for the adequate collection, storage, and sharing of samples and data for research.

Collecting and sharing human biological samples and data of individuals for future research unethically undermines trust, which is necessary for people to be willing to donate samples and data for research purposes. Therefore, in consideration of well-being and respect for persons and populations, it is important to ensure that samples and data are used in accordance with the terms in which they were provided and that confidentiality is safeguarded. Furthermore, to ensure that samples and data are shared fairly and responsibly, future research should take into account the interests and needs of the population that provided them, which can result in additional challenges if the samples and data are transferred overseas as part of international collaborations. In these cases, proper recognition should also be sought for researchers and other local counterparts for their contribution to the conduct of these studies.

In sum, to catalyze ethical research that improves the health and wellbeing of populations, ethical sharing of samples and data must be encouraged in health emergencies as well as in non-emergency situations. This entails responsibilities at different points in the process: during the collection, storage, transfer, and future use of samples and data in research projects.

6.1. Broad informed consent processes to collect samples or data for future research

The collection of samples or data for research purposes should be carried out with the informed consent of individuals, even though health emergencies may entail practical difficulties for informed consent processes. A broad informed consent process allows for the use of samples and data in future research that is not yet conceptualized or planned but may be conceived as new information becomes available. This differs from a specific informed consent process which seeks participation in a particular study whose protocol is already developed.

Like any informed consent process that is conducted in health emergencies, processes to obtain broad informed consent for future research should be adapted to the circumstances and needs of the emergency in question. Additionally, as established by the CIOMS guidelines 11 and 12 ([1](#)), at least the following information should be provided:

- who will be responsible for the storage of samples or data, and how long they will be stored;
- the conditions for future use in research (for example, for use only in emergency-related research or for research that is not related to the emergency);
- that future research will be previously reviewed by a REC;
- the measures taken to protect confidentiality;
- the possibility of being contacted for the disclosure of incidental findings;
- the options for withdrawing consent and samples or data, including the impossibility of doing so if all individual identifiers were removed when storing them, making it impossible to associate people with the samples or data they provided.

Every study using individually identifiable samples or data that were previously collected through a broad informed consent process must be reviewed and approved by a REC. The committee should ensure that the proposed use aligns with what the person authorized by giving consent and adheres to ethical standards. If the proposed uses do not correspond to what people authorized when their samples or data were collected, or if broad consent for future research was not obtained, RECs may require recontacting individuals whose samples or data will be used in order to obtain a new consent or analyzing whether it is appropriate to grant a waiver of consent (box 10).

Box 10. Criteria for obtaining a waiver of informed consent

RECs can approve a waiver of informed consent for a study if these three conditions are met:

- it is not feasible to conduct the study without the waiver;
- the study has an important social value; and
- it poses only minimal risks to participants.

REC: Research ethics committee.

Source: Council for International Organizations of Medical Sciences. International ethical guidelines for health-related research involving humans. Fourth edition. Geneva: CIOMS; 2016. Available from: <https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf>.

For situations in which the samples or data are obtained from health care settings (e.g., residual tissues used for clinical diagnosis) or public health surveillance, it may be appropriate to conduct an informed opt-out procedure. This means that, instead of asking a person to allow the use of their samples and data for future research, they are informed about this intended use and invited to indicate if they do *not* want their data or samples to be used in research. If so, their samples or data are withdrawn. In order to be ethically justifiable, the informed opt-out procedure should meet certain conditions (box 11). Nevertheless, there are circumstances in which this consent process is not appropriate (box 12).

Box 11. Conditions for informed opt-out procedure for future research with samples or data

An ethically acceptable informed opt-out procedure for future research with samples or data must meet the following conditions:

- people should be informed about this process;
- sufficient information should be provided;
- options to withdraw their samples or data on demand (except when the removal of all individual identifiers is planned) are explained; and
- refusal to participate is a genuine possibility.

Source: Council for International Organizations of Medical Sciences. International ethical guidelines for health-related research involving humans. Fourth edition. Geneva: CIOMS; 2016. Available from: <https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf>.

Box 12. Scenarios in which an informed opt-out procedure for future research with samples or data is not appropriate

An informed opt-out procedure for future research with samples or data is inadequate in these scenarios:

- the research involves more than minimal risks;
- controversial or high-impact techniques are used;
- the research is conducted with certain types of tissues (e.g., gametes); or
- the research is conducted in contexts of heightened vulnerability.

The REC should determine whether it is ethically acceptable to use an informed opt-out procedure for future studies or whether, on the contrary, an explicit informed consent process (specific or broad) for research is necessary.

REC: Research ethics committee

Source: Council for International Organizations of Medical Sciences. International ethical guidelines for health-related research involving humans. Fourth edition. Geneva: CIOMS; 2016. Available from: <https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf>.

6.2. Storage, transfer, and future use of samples and data for research

In order to ensure that samples and data are stored ethically for use in future research, governance mechanisms are needed to ensure that the quality of the samples and data is preserved, and future uses are in accordance with what was authorized by the people who provided those materials. This includes obtaining REC approval for each research protocol that plans to use stored samples or data, and having procedures in place for those who donated data or samples to withdraw their consent for the use of their data or samples in future research. It also includes provisions for people who donated data or samples to be contacted with information about research results or incidental findings as established by the CIOMS ethical guidelines (1).

Future research may be conducted at institutions other than those that collected or stored the samples or data. Transfer of samples or data to other institutions must proceed in accordance with what was authorized by the people who provided their samples and data, for which Material Transfer Agreements or Data Transfer Agreements between the institutions should be used. These agreements are legal contracts that establish the terms of use of the samples and the data being transferred, in order to ensure the fulfillment of prior ethical commitments made to people and their communities and, ultimately, the protection of their rights, interests, and wellbeing. They further ensure that the institution and researchers responsible for storing the samples and data are acknowledged and treated fairly.

It is key to ensure that individuals and communities that contributed to research by providing samples and data are treated fairly. This becomes increasingly concerning when the studies are conducted in the distant future or in foreign countries. Indeed, it is concerning that when countries collaborating in research have very different capacities to look after the wellbeing or interests of their populations, these differences may lead to unfairness, either because those who contributed samples and data for the research will not enjoy its potential benefits or because they are expected to bear a disproportionate burden for the benefit of others. In health emergencies, unfairness may result from undue delays in benefitting from research, which may entail harms to health or wellbeing that should have been avoided.

In all cases, those who contributed to research should be treated fairly. This implies discussing and agreeing in advance how the benefits derived from research will be allocated. Such benefits may include access to the resulting health technologies or the knowledge to replicate those technologies, a share of intellectual property rights or economic benefits generated from their commercialization, or academic recognition to institutions or professionals for their contribution collecting and storing samples and data for the production of knowledge (including authorships and collaborations in publications as relevant). Moreover, institutions or jurisdictions that contribute to the collection and storage of samples or data may make agreements with their international counterparts on plans to strengthen their research capacity or infrastructure, with a view to ensuring fair contributions.

A fair return for research contributions is essential to safeguard and strengthen the public's trust in research, in research institutions, and in the health authority tasked with ensuring that research is conducted ethically. To the extent that a fair return entails considering the needs and priorities of those who provided samples and data for future research, RECs should include representatives from those specific communities when reviewing research proposals. RECs should also establish communication channels to understand the concerns of the population and respond to them, or to make inquiries about future research, if necessary. This is particularly important if samples or data will be stored for a long period of time. Furthermore, to advance public engagement, the public needs to receive reliable information about the approved studies, the results and benefits of research, the importance of sharing samples and data for future research, and the safeguards to conduct it ethically. Finally, especially in emergency situations, health authorities should be involved in the planning process and in establishing what is owed to populations in order to ensure a fair and timely return for their contribution to research.

CHAPTER 7.

FINAL RECOMMENDATIONS

Following several regional dialogues (box 9) and continued critical reflection with national authorities, RECs members, researchers, and ethicists from the Region, a series of final recommendations has been prepared, with a view to improving our ethical preparedness for future emergencies and strengthening research ethics in general. These recommendations constitute our pending regional agenda and supplement the specific recommendations on each topic for which this document provides guidance. They are divided into recommendations for action, which can be implemented immediately, and recommendations to further conceptualize the specific actions needed to put them into practice. In both cases, the final recommendations may be relevant only to health emergencies or may apply to both emergency and non-emergency situations. Recommendations for emergency situations involve actions that must be implemented before a health emergency occurs, as part of emergency preparedness. Recommendations that apply beyond emergency scenarios entail actions to strengthen research ethics in ordinary situations; as a result, their implementation should not be limited to health emergencies, although their impact may be greater in emergency situations due to the role of research in emergency response.

Table 9. Classification of final recommendations

Type	Recommendations specific to health emergencies	Recommendations for ordinary situations, including health emergencies
Recommendations for action	Actions for health authorities, the scientific community, and international organizations.	Actions for health authorities, RECs, institutions that conduct research, the scientific community, and international organizations.
Recommendations for conceptualization	All parties involved, including academia and people who study research processes (e.g., those working on postgraduate theses or dissertations related to research and ethics).	

REC: Research ethics committee

7.1. Recommendations for action

7.1.1. For health emergencies

- 1. Health authorities** should establish strategies for the oversight of research ethics in future health emergencies, which include procedures for prompt and rigorous ethics review and monitoring. For this purpose, they should:

- a. Consider the relevance of combining strategies as appropriate to the duration of the emergency. A strategy for short-term emergencies may be envisaged, with provisions for migrating to a different strategy with different procedures if the emergency is prolonged or worsens.
 - b. Formalize the chosen strategies through the appropriate legal instruments.
 - c. Allocate the necessary resources to implement the chosen strategy efficiently and sustainably for the duration of the health emergency.
 - d. Establish rapid communication mechanisms between the RECs and the national authorities to be activated as part of the strategy.
2. **The scientific community, international organizations, and health authorities** should develop generic research protocols for potential health emergencies (also called *master protocols*, such as the ones developed during the Zika outbreak (43), which harmonize key methodological aspects. It is recommended to include an ethicist when designing these protocols and submit them to a REC for preliminary ethics approval. As soon as an emergency occurs, these protocols should be adapted as necessary, and the final versions must be reviewed and approved rapidly by the REC.
 3. **Health authorities** should entrust the relevant research authorities (e.g., the National Institute of Health or the Research Office within the Ministry of Health) with responsibility for coordinating research efforts in emergencies. This includes establishing research priorities and networks of experts.
 4. **Health authorities** should designate a person who serves as a contact point for research as part of the national incident response team that is established during every health emergency.
 5. **Health authorities** should establish processes for involvement in the research conducted in response to health emergencies from the beginning in order to ensure that countries and their populations benefit from their potential results.

7.1.2. For ordinary situations, including health emergencies

1. **Research ethics committees and health authorities** should review their procedures to incorporate virtual tools (e.g., use of online systems for the review of research), as well as agile communication and coordination mechanisms with other RECs and regulatory authorities. To this effect, the documents or regulations that govern the operation of RECs should be modified and their capacities and resources strengthened, as necessary.
2. **Research ethics committees and health authorities** should allow for different ways of carrying out informed consent processes, so that they are not limited to face-to-face processes in which willingness to participate in a study is expressed in writing and on paper. To this effect, the documents or regulations that govern these processes should be modified, as needed.
3. **Research ethics committees and health authorities** should establish clear and agile procedures to determine which activities constitute research with human subjects and thus require REC review. This will make it easier for epidemiological surveillance and other public health activities to avoid being erroneously treated as research and to promote their adherence to the appropriate ethical framework.
4. **Research ethics committees** should require that researchers submitting a proposal for review report prior reviews conducted by other (local or international) RECs and, if so, include a copy of their decisions.

5. **Research ethics committees** should establish communication mechanisms (e.g., through social media) if it becomes necessary to inform the public about studies they are supervising.
6. **Institutions (whether public or private) that conduct research** should compensate REC members financially or through another appropriate formal mechanism for their time and dedication (e.g., counting the hours assigned to the REC as hours worked), in the same way that other parties involved in research (such as researchers and health authority staff) are recognized. Compensating REC members recognizes the key role of RECs in the ethical conduct of research. Furthermore, it helps them to carry out their tasks with the necessary speed and rigor, paving the way to a more professional approach to the work of RECs. Such compensation mechanisms should be considered as part of the health authority's REC registration and accreditation processes.
7. **Health authorities** should establish information and coordination mechanisms to gather information about studies that were submitted for REC review and not approved, and, if necessary, share this information (with the corresponding decisions) with other RECs that are asked to review the same protocol.
8. **Health authorities** should formally require all clinical trials to be registered in registries that feed ICTRP before they begin. This requirement could be formalized through a legally binding instrument (such as a Ministerial Resolution) and should apply to all clinical trials, not just those on drugs and devices.
9. **Health authorities** should establish in each jurisdiction a publicly accessible website that lists the studies with human participants that have been approved. For clinical trials, reference to the registration in an ICTRP registry should be included.
10. **Health authorities** should assume responsibility for continually informing the public about the research conducted, e.g., through social media or other strategies identified by their communications offices, in order to facilitate public engagement and promote trust in research and in the knowledge that results from it. With a view to a better understanding of research and the ways to ensure it is conducted ethically, scientific journalism should be strengthened and spaces to disseminate scientific research in the media should be encouraged.
11. **Health authorities and international organizations** should advocate for expanding the scope of ICTRP so that it includes all research with human participants and not only clinical trials, which will allow for the global implementation of the stipulations from the 2013 Declaration of Helsinki.
12. **National authorities, international organizations, research ethics committees, and the scientific community** should strengthen capacities in research ethics, particularly in relation to the distinction between research with human subjects and public health activities, emergency use of unproven interventions outside of research (MEURI framework), ethical use of samples and data in future research (including the importance of avoiding the destruction of samples and using material and data sharing agreements), adaptive designs, human challenge studies, online studies, scientific integrity, and the REC's obligations regarding what must be kept confidential and what must be made public.

7.2. Recommendations for conceptualization

7.2.1. For health emergencies

1. Design and implement mechanisms for effective coordination of research efforts initiated in emergencies, in order to know which initiatives are underway and who is responsible for them

before studies are registered. This, in turn, will prevent the duplication of research and make collaboration possible (e.g. by conducting network trials or multicenter studies).

2. Plan a strategy to generate collaborations within the Region to conduct research in emergencies that addresses the logistical challenges posed by conducting regional multicenter clinical trials during health emergencies, and the legal instruments that may be needed to implement those trials.
3. Develop mechanisms for the ethics oversight of research at the (sub)regional level (e.g., using the strategy of extraterritorial ethics oversight during health emergencies).

7.2.2. For ordinary situations, including health emergencies

1. Design and implement strategies that streamline the review and monitoring carried out by multiple RECs, either through coordination mechanisms (which may involve the review of different RECs in a simultaneous deliberation) or by establishing mechanisms that allow a REC to adopt the review carried out by another, without the need to repeat the review process (e.g., through previous reliance agreements).

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ANNEX 1. TEMPLATE OF STANDARD OPERATING PROCEDURES FOR THE ETHICS OVERSIGHT OF RESEARCH RELATED TO HEALTH EMERGENCIES

1. Internal organization of research ethics committees

1.1. Composition of the research ethics committee

For the ethics oversight of research related to the emergency, the REC must have (*increased number*) of members and include health professionals with knowledge relevant to the health emergency, methodologists, pharmacologists, ethicists, and representatives of the community, ensuring multi-disciplinarity and gender diversity among members.

The REC chair must identify and ensure that members reviewing protocols have the availability that is needed for rapid reviews and basic knowledge about the ethics of research in emergency situations.

1.2. Selection of members for the review of each proposal

The selection of members who will review each proposal should be made based on their knowledge and experience relevant to the protocol. Before selecting members to review protocols, they should be consulted about their availability to conduct a rapid review through digital tools.

1.3. Selection and recruitment of independent consultants

The REC may seek advice from independent consultants, as necessary, based on the topic or complexity of the research proposal, or when the REC does not have the necessary expertise for its review. If appropriate, consultants may also act as *ad hoc* members, with full decision-making capacity.

The REC maintains a list of independent national or international consultants who have been previously identified based on their expertise pertaining to the health emergency and their availability to review proposals. The chair (or whomever assumes that role) should convene the independent consultants, at the request of the REC, using digital tools. Consultants must sign a declaration of conflicts of interest and a confidentiality agreement before receiving any documentation.

1.4. Digital registry and documentation archive

REC documentation will be filed digitally in (*secure hosting service in the cloud or other digital platform*). The Secretariat is responsible for those files, to which all REC members will have access.

Documentation received by the REC, electronic or digitized minutes, and reports, as well as any other information generated as part of the review and monitoring processes, must be kept in the digital archives.

1.5. Responsibilities of members

The responsibilities of members are to:

- 1.** Provide the REC with an email address and a mobile number, and commit to checking the messages and the electronic platform used by the REC on a daily basis.
- 2.** Respond to the chair's requests in a timely manner.
- 3.** Review the protocols within the established deadlines and send the corresponding reports.
- 4.** Attend virtual meetings or, if this is not possible, send comments, including the relevant justifications, via email or through the platform used by the REC.
- 5.** Conduct ethics monitoring as decided by the REC.
- 6.** Review protocols for emergency use of unproven interventions outside of research.
- 7.** Other duties necessary for the proper functioning of the REC during the emergency.

1.6. Responsibilities of the Secretariat

The responsibilities of the Secretariat are to:

- 1.** Provide information on the SOPs of the REC during the emergency (requirements for submitting applications and internal processes of the REC, among other aspects) to researchers, sponsors, and the health authority.
- 2.** Register the documentation sent to the REC through digital tools and coordinate its management with the chair.
- 3.** Manage the timely progress of research protocol reviews through close communication with members and researchers.
- 4.** Prepare the REC meetings. This includes distributing relevant documentation to members, scheduling meetings, and ensuring quorum.
- 5.** Prepare the minutes, decisions, and any other necessary documentation of the REC in coordination with the chair (or whomever assumes that function).
- 6.** Request the registration of studies in a registry that feeds ICTRP.
- 7.** Maintain the archive of records and documentation, with guaranteed confidentiality of the information.
- 8.** Other duties necessary for the proper functioning of the REC during the emergency.

1.7. Responsibilities of researchers

The responsibilities of researchers are to:

1. Provide an email address and mobile phone number, committing to checking messages daily and answer calls from the REC.
2. Submit the requests for initial review, progress reports, reports of adverse events, amendments, and any other information, as established by the REC.
3. Respond to the REC's requests within the established deadlines and according to the REC's SOPs.
4. Conduct research in adherence to international ethical standards and national regulations.
5. Carry out studies in accordance to the approved protocol, except when immediate action is necessary to prevent harm to participants.
6. Comply with the monitoring plan established by the REC.
7. Review the available scientific evidence periodically and in a timely way in order to update their knowledge related to the research. If new evidence arises that could affect the conduct of a study, researchers must immediately notify the REC and submit a report justifying how to proceed in response to that evidence (i.e., continuation, modification, suspension, or cancellation of the study).
8. Register their research in a registry that feeds the ICTRP.
9. Continuously inform participants, using friendly language, about the progress of the study including emerging scientific evidence and study results.
10. Submit final reports of studies to the REC.
11. Other duties necessary for the ethical conduct of the research during the emergency.

2. Ethics review process

2.1. Submissions for review

Requests for review of research projects related to the emergency are prioritized.

The protocol and all its documentation are submitted through (*email or name of the platform used by the REC*).

If the submitted documentation is incomplete, the researcher will be notified and given a deadline to provide the missing documents. The review process starts as soon as the essential documentation is received.

Submissions of amendments to a protocol, reports or any other communication must be sent through (*email or name of the platform used by the REC*). Submissions of amendments must include a description of the amendments, their justification, the final version of the amended document, and the version with track changes.

Progress reports are presented according to the terms established in approval decisions.

Reports on protocol deviations, adverse events, adverse reactions, and safety must be submitted within 48 hours of their occurrence, indicating the reasons and measures that were adopted in response.

The final research report of the study is presented when finalizing the study.

2.2. Documents for initial review

For the initial review of emergency-related research, the researcher should present to the REC, in addition to the ordinary requirements, the following documentation in the language of the country:

- a summary of the study in non-technical language (maximum two pages);
- up-to-date, previously published evidence, if available;
- the plan for minimizing risks of infection and saturation of the health system;
- samples or data sharing plans, if any;
- the plan for the publication and dissemination of the results, indicating the process by which they are communicated to the public and health authorities; and
- the decisions of other RECs that have reviewed the research proposal.

In the case of clinical trials, the following should also be presented:

- for multicenter projects, authorizations of the (national or international) regulatory authorities, as applicable;
- list of sites in the country where the clinical trial is to be conducted, as applicable; and
- the plan for making available to the participants and the public any intervention that has been found effective.

2.3. Initial review of studies by members

The protocol and all its documentation should be assigned to at least two members for review.

Documents for review are sent via..... (*email or name of the platform used by the REC*) to members within 24 hours of receiving the request for review.

Members have a period of 72 hours to conduct their review after receiving the request. The deadline may be longer depending on the complexity of the study. Review reports (inclusive of the relevant justifications) are submitted through (*email or name of the platform used by the REC*).

2.4. Quorum

The quorum for making decisions on research protocols or other requests is (*half plus one, $\frac{1}{3}$*) of the total number of members. It should include members with experience and knowledge relevant for the review of the research in question.

If members are unable to participate in the virtual meeting, they will be considered for quorum if they submit their reviews electronically.

2.5. Virtual meetings

Virtual meetings to deliberate and decide on research protocol related to the emergency will be scheduled within 24 hours of receiving the members' reports. The Secretariat will communicate electronically the exact date and time of the meeting to REC members and consultants (if applicable),

The Secretariat will also communicate the date and time of the meeting electronically to researchers so that, if possible, they are available if their virtual participation is required to quickly clarify any doubt that the REC may have.

During the meeting, the Secretariat, in coordination with the chair (or whomever assumes that role), must take notes on the deliberations and decisions on the research protocols, including who attended the meeting, quorum requirements, the decisions adopted (i.e., approval, conditional approval, or non-approval) and the reasons supporting decisions, among other issues.

2.6. Staggered review and decision-making

If a virtual meeting cannot be organized in a timely manner, the review, deliberation, and decision-making may be staggered.

The chair (or whomever assumes that role), in coordination with the Secretariat, sends the review reports to REC members by email or through the electronic platform of the REC. Members will send their comments and observations electronically, by phone, or by text message.

The REC endeavors to make decisions by consensus. If this is not possible, decisions will be made by a majority of members.

2.7. Communication of the decisions of the research ethics committee

All requests to researchers, REC decisions, and other communications are sent through.....
(*email or name of the platform that the REC uses*).

The REC communicates its decisions to researchers within 24 hours. Researchers must respond to the REC within 48 hours.

Communications to the relevant institutions and authorities and to the other RECs must be sent as soon as possible.

REC communications and decisions can have the signature of the chair alone (or whomever assumes that role).

2.8. Additional reviews

Amendments and reports will be reviewed by members who reviewed the original protocol. Documents should be reviewed within 24 hours of receipt. If more information is required, it will be requested from the principal investigator within the same time period.

Members should respond within 48 hours from receipt of the documentation. The response is sent through..... (i.e., *email or name of the platform used by the REC*) and communicated to the principal investigator within 24 hours.

2.9. Protocols for the emergency use of an unproven intervention outside of research

Any emergency use of unproven interventions offered outside of research must be reviewed by the REC prior to initiation. The use will be proposed through a protocol that includes at least the following elements:

- background;
- scientific justification on the basis of the recommendations of a scientific committee;
- objectives;
- population to be offered the intervention;

- risks and potential benefits;
- measures to minimize risks;
- scientific data to be collected that may provide information on the intervention's safety and efficacy;
- plan to offer the intervention;
- informed consent documents and details about the process;
- measures to protect confidentiality;
- data sharing plan; and
- proposal for the transition to research.

The REC reviews the protocol and evaluates whether the proposed emergency use of the unproven intervention adheres to the ethics criteria for its justification, ethical and regulatory oversight, informed consent, and contribution to the generation of evidence established in the MEURI framework. The REC must consider at least the following aspects:

- available scientific evidence justifies the intervention, based on its risk-benefit balance;
- the intervention is offered to the appropriate population;
- measures to minimize risks;
- informed consent process is adequate and in accordance with the emergency context. It specifies that the intervention has not been proven and explains what it consists of, along with its risks and potential benefits and the data that will be collected;
- data that will be collected are relevant to provide information about the safety and efficacy of the intervention;
- measures to safeguard the confidentiality of the data that have been taken;
- establishment of a procedure to rapidly share data with the health authorities, and the national and international scientific community; and
- proposed transition to offer the intervention as part of research.

Once the protocol to offer an intervention under the MEURI framework has been approved, the REC must request its registration in registries that feed ICTRP and in any other registry that is required locally. If mechanisms have not been implemented in the registries to distinguish the interventions offered under the MEURI framework, the title of the protocol should state it.

3. Ethics monitoring

3.1. Monitoring of research

Ethics monitoring should be carried out more frequently through reports submitted by the researcher. It can be carried out remotely or deferred in accordance with the established deadlines, protecting the confidentiality of the information.

The chair may designate a REC member or group to be in charge of monitoring a particular research protocol.

3.2. Monitoring in response to emerging evidence

After the research has been approved, the REC must guarantee that it continues to be ethically acceptable during its conduct, on the basis of the most up-to-date available evidence.

Researchers must review the available scientific evidence periodically and in a timely manner in order to update their knowledge related to their research. If new evidence emerges that could affect the conduct of their research, researchers must evaluate it and promptly send the REC a report that includes the most important points of the review carried out, the references consulted and the justification for the way in which they will proceed (whether the study will be continued, modified, suspended, or terminated).

The REC reviews the protocol on the basis of the new evidence and approves, as appropriate, the measures proposed by the researchers. Regardless of such measures, the REC may request additional measures, and even temporarily suspend or cancel the study.

The REC communicates its decision immediately to the relevant health authorities and publishes it on its website. In addition, it should request researchers to record any change to the study, as soon as possible, in the respective research registries, including those that are part of the ICTRP.

3.3. Monitoring the emergency use of unproven interventions outside of research

For the monitoring of the emergency use of an unproven intervention offered outside of research, the REC will request that the health professional responsible for the intervention submit periodic reports evaluating whether the intervention continues to be justified on the basis of the new evidence. The REC may require modifications to the intervention or the way it is offered, as well as its suspension or termination.

ANNEX 2. GUIDING QUESTIONS TO FACILITATE ETHICS REVIEW OF EMERGENCY USE OF UNPROVEN INTERVENTIONS OUTSIDE OF RESEARCH

1. First step: Is the use of this intervention ethically justifiable?

1.1. Ethics criterion 1: Justification

1. Is it a public health emergency that could have a severe impact on people's health, regardless of the geographic reach of the affected area?
2. Is there any safe and effective intervention to prevent or treat these severe health impacts?
3. Is there any intervention that, although unproven for the disease in question, is recommended by qualified scientists based on preliminary evidence supporting their safety and efficacy?
4. What is the risk-benefit profile of the intervention under the proposed conditions?
5. What is the position of PAHO or WHO, and other relevant scientific committees, regarding the use of this intervention in this context?
6. What is the reason this intervention is not being offered as part of research, for example, within a clinical trial to quickly find out if it is safe and effective?

2. Second step: If the use of this intervention is justified, how can we proceed to ensure that its use is ethical?

2.1. Ethics criterion 2: Ethical and regulatory oversight

1. Has a REC approved the protocol to offer the intervention in question outside of a study?
 - a. Has it evaluated whether the use of the intervention is justified on the basis of the available evidence and the risks and potential benefits?
 - b. Has it evaluated the relevant ethical aspects, including the informed consent process?
 - c. Has it evaluated whether it will contribute to the generation of knowledge despite not being part of a study?
2. Has the national regulatory authority or other competent national authority approved the protocol to offer the intervention in question outside of a study?
 - a. Has it determined that the information collected is useful in contributing to knowledge about the safety and efficacy of the intervention?
3. Is the national regulatory authority or other competent national authority monitoring safety, for example by ensuring that products used are made in accordance with good manufacturing practice?
4. Has the protocol been registered in the corresponding public registries, specifying that it is not a research study but an emergency use outside of research?

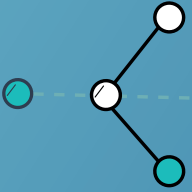
5. Do a REC and the regulatory authority monitor the use of the intervention after it has been approved, to ensure that it is still justified to offer?
6. Is there a plan to offer the intervention as part of a research study within a set time frame?

2.2. Ethics criterion 3: Informed consent process

1. Is there an adequate informed consent process that allows persons (or their representatives) to decide voluntarily if they want to receive the unproven intervention outside of a research protocol?
2. As part of the consent process, are people informed that the intervention might not benefit them and might even harm them?
3. Is the public being informed about the unproven intervention, with the specification that it is not known to be safe and effective?

2.3. Ethics criterion 4: Contribution to the generation of evidence

1. Are the data that are considered essential to contributing to knowledge about the intervention being collected in a systematic way?
2. Are these data being shared in a timely and transparent manner with the health authority and the scientific community?



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