

Emergency use of unproven interventions outside of research Ethics guidance for the COVID-19 pandemic

Introduction

The COVID-19 pandemic presents us with the moral urgency to conduct rigorous research as soon as possible to produce evidence about the safety and efficacy of interventions to treat or prevent COVID-19 (1). However, as in previous emergencies, marked by high mortality and the absence of safe and efficacious treatments, interventions that have not been previously proven for COVID-19 are being offered outside of protocols of research with human subjects. Under normal circumstances, interventions are first tested as part of research studies that aim primarily at producing knowledge. A number of procedures are in place to ensure that research participants are adequately protected and quality data are collected. After the necessary studies have been completed, and interventions have been proven and established as safe and efficacious through rigorous processes led by a National Regulatory Authority (NRA), they are authorized and can be provided to patients to treat or prevent diseases.

During the pandemic, interventions that have not been proven safe and efficacious for COVID-19 are being offered outside of research contexts. That comprises diverse interventions, ranging from drugs (e.g. ivermectin) to blood products (e.g. convalescent plasma), and including interventions that have been proven safe and efficacious for a condition other than COVID-19 and thus authorized (e.g. hydroxychloroquine), and interventions that have not been proven effective nor authorized for another condition (e.g. remdesivir). Since the safety and efficacy of these interventions have not been proven for COVID-19 yet, their risk-benefit profile is unknown. Yet in the exceptional circumstances of the pandemic, they are being offered as an attempt to advance access to interventions that *may* benefit patients. As recommended by the Pan American Health Organization (PAHO) and the World Health Organization (WHO), unproven interventions should be offered within research protocols, and specifically within randomized controlled trials capable of assessing safety and efficacy (2, 3, 4). In the exceptional circumstances in which this recommendation cannot be followed, and access to unproven interventions is offered outside of research, their use must be conducted under an ethical framework that ensures adequate ethical and regulatory oversight while contributing to the generation of evidence.

Objectives

This guidance document has the following objectives:

- (1) Present the existing framework aimed at ensuring that the use of unproven interventions outside of research during an emergency is ethical.

- (2) Discuss the challenges encountered in the use of unproven interventions outside of research during the COVID-19 pandemic in the Region of the Americas.
- (3) Provide general and operational recommendations to advance during the COVID-19 pandemic the ethical use of unproven interventions outside of research.

This document does not address the use of unproven interventions outside of the context of the COVID-19 pandemic, i.e. off-label use for non-COVID-19 situations. It is not meant to be of relevance for situations that may constitute a clinical urgency for one person, when such urgency is not part of a public health emergency. Finally, while the document is relevant for the use of convalescent plasma as one of the unproven interventions that is being offered outside of research settings for COVID-19, it does not address the specific challenges posed by the fact that in some jurisdictions blood products are not overseen and regulated by NRAs as PAHO and WHO recommend. In those jurisdictions, the relevant national health authorities must ensure adherence to the standards presented in this guidance.

1. Emergency use of unproven interventions outside of research: Ethical criteria

In response to extraordinary challenges encountered during the 2014 Ebola outbreak, the World Health Organization (WHO) devised criteria to determine under which conditions it can be ethically appropriate to offer unproven interventions outside of research, and referred to this framework as “monitored emergency use of unregistered and experimental interventions” (MEURI) (5). MEURI aims at offering affected persons access to these interventions in view of their *possible* benefit, while ensuring that their use is monitored and contributes data to the generation of evidence. Robust clinical trials are still needed in order to demonstrate the safety and efficacy of these interventions.

During the COVID-19 pandemic, PAHO and WHO have stressed the urgency of conducting rigorous research to devise safe and efficacious preventive and therapeutic interventions, and the imperative to adhere to ethical guidance if unproven interventions are exceptionally offered outside of research (2, 3, 4). The criteria to determine if it is ethically acceptable to offer unproven interventions outside of research in these exceptional circumstances are the following:

- 1) *no proven effective treatment exists;*
- 2) *it is not possible to initiate clinical studies immediately;*
- 3) *data providing preliminary support of the intervention’s efficacy and safety are available, at least from laboratory or animal studies, and use of the intervention outside clinical trials has been suggested by an appropriately qualified scientific advisory committee on the basis of a favorable risk–benefit analysis;*
- 4) *the relevant country authorities, as well as an appropriately qualified ethics committee, have approved such use;*
- 5) *adequate resources are available to ensure that risks can be minimized;*
- 6) *the patient’s informed consent is obtained;*

- 7) *and the emergency use of the intervention is monitored and the results are documented and shared in a timely manner with the wider medical and scientific community (5).*

These seven criteria can be categorized and supplemented with additional guidance provided by WHO (5) to elucidate the MEURI framework as follows:

Justification	
<p><i>1. No proven effective treatment exists.</i></p> <p><i>2. It is not possible to initiate clinical studies immediately.</i></p> <p><i>3. Data providing preliminary support of the intervention's efficacy and safety are available, at least from laboratory or animal studies, and use of the intervention outside clinical trials has been suggested by an appropriately qualified scientific advisory committee on the basis of a favorable risk–benefit analysis.</i></p>	<ul style="list-style-type: none"> • The emergency use of unproven interventions can be ethical in exceptional circumstances characterized by high mortality and the absence of proven therapeutic options to offer patients available and reasonable opportunities to improve their health condition. • A rigorous scientific assessment of the available evidence must be conducted by an appropriately qualified scientific committee, which must determine if the proposed intervention has a favorable risk-benefit profile and thus can be considered for use under MEURI. • MEURI must not be used as a means to circumvent ethical oversight of the use of unproven interventions, or to avoid conducting clinical trials when it is feasible to do so. Indeed, at this point of the pandemic, and considering that numerous clinical trials have been already initiated or are being initiated in the majority of countries in the Region, it is increasingly difficult to argue that clinical trials (or other types of clinical studies) cannot be initiated.

Ethical and regulatory oversight	
<p><i>4. The relevant country authorities, as well as an appropriately qualified ethics committee, have approved such use.</i></p> <p><i>5. Adequate resources are available to ensure that risks can be minimized;</i></p>	<ul style="list-style-type: none"> • MEURI requires the review and approval of an ethics committee and the NRA, along with other relevant national authorities, which will vary based on the local norms and the type of intervention at stake. • While MEURI does not constitute research but rather access to an unproven intervention outside of research, it should be guided by the same ethical principles that govern the use of unproven interventions in clinical trials. A research ethics committee (REC) must thus conduct the review. Only investigational products manufactured according to good manufacturing practices should be used for MEURI.

Consent process	
<p><i>6. The patient's informed consent is obtained.</i></p>	<ul style="list-style-type: none"> • Patients should voluntarily decide, based on their own assessment of risks and benefits, if they want to receive the intervention offered as MEURI. • Patients must be informed in a clear way that the intervention being offered has not been proven, so it might not benefit them and may even harm them. As in other circumstances, proxy consent should be obtained as appropriate. • National health authorities should provide the information about the risks and potential benefits of interventions that have not been proven safe or efficacious, and promote dialogue about MEURI with the goal of advancing clarity and avoiding false perception of benefits. This community engagement is key, particularly in the context of the pandemic, for meaningful consent processes.

Contribution to the generation of evidence	
<p><i>7. The emergency use of the intervention is monitored and the results are documented and shared in a timely manner with the wider medical and scientific community.</i></p>	<ul style="list-style-type: none"> • While MEURI aims at offering patients access to unproven interventions given the absence of proven therapeutic options, MEURI must contribute to the generation of knowledge, which is urgently needed in the context of the pandemic. • Health care professionals responsible for MEURI protocols have the same moral obligation to collect all scientifically relevant data that may provide information on the safety and efficacy of the intervention as researchers overseeing a clinical trial, and to share them in a timely manner. • Close coordination with national authorities is essential to identify meaningful data to be collected and shared without delay, accurately and transparently with all relevant national and global stakeholders. • It is essential to aggregate knowledge through MEURI, advancing its use as part of protocols or programs offering access to a large group of patients (instead of to single patients). This allows for systematic and efficient data collection and avoids posing an undue burden on national authorities and RECs that are already overstretched in the pandemic.

2. Challenges during the COVID-19 pandemic of the use of unproven interventions outside of research

A key challenge posed by the use of unproven interventions outside of research during the pandemic in the Region of the Americas is the absent or limited adherence to the existing ethics guidance for MEURI, which can be attributed to a lack of familiarity with this guidance and the particularly dire conditions of the pandemic. The complex correlation of MEURI to varying regulatory nomenclatures (e.g. expanded use, compassionate use), that may even be entirely absent in some jurisdictions, is further challenging. Moreover, the MEURI framework can be seen as intrinsically complex: while MEURI is defined as non-research and aims at offering patients access to an intervention that *might* benefit them, it calls for a contribution to the production of evidence and for prior ethics review as is done in research.

From a practical perspective these challenges get exacerbated because clinical trial registries and other research registries do not allow easy differentiation between an intervention being provided as MEURI or as research. Furthermore, in the context of the pandemic some interventions offered as MEURI are collecting a more extensive set of data than some clinical trials planned in response to the need to avoid contagion and additional burdens to health care providers. The lack of implementation of the MEURI framework implies that interventions are being offered without meeting one or many of the criteria above, that is, without adequate justification, without ethical and regulatory oversight, without adequate informed consent, and without contributing to the generation of evidence.

Challenges posed by the lack of implementation of the MEURI framework. Two specific challenges are prominent in the Region of the Americas:

1) *Unjustified use of unproven interventions*

- Interventions that are not justified on the basis of available evidence are being offered. This implies using limited resources on interventions with a poor risk-benefit profile, which may come at the expense of using those resources in a way that can positively impact health (e.g. acquiring masks).
- Offering an unproven intervention outside of research is unjustified if it is possible to offer it as research. The high number of registered clinical trials from the region shows the increasing feasibility of conducting research. Research (and primarily randomized controlled trials) should be prioritized because of their capacity to contribute rapidly to the generation of robust evidence.
- The use of unproven interventions without a prior assessment of their justification leads to abusing a scenario that was conceived as an exceptional case within a public health emergency. Its generalized use entails the risk of the false perception among the population that the intervention is indeed beneficial, which in turn hampers consent processes.

2) Lack of adequate ethical and regulatory oversight

- Challenges range from the lack of prior approval from an ethics committee and the national health authority to the involvement of both without clarity about their role for MEURI's exceptional circumstance. Adequate ethical and regulatory oversight ensures that the intervention is justified, the integrity of consent processes and the contribution to the generation of evidence. Monitoring of MEURI is key during the pandemic because evidence is volatile.
- Lack of clarity about the oversight that corresponds to MEURI has led to practices such as characterizing MEURI as "observational research." This generates additional confusion because MEURI by definition is not research and further opens the door to characterizing activities that involve interventions in ways that allow evasion of the corresponding ethical and regulatory oversight.

3. Recommendations for the use of MEURI during the COVID-19 pandemic

General recommendations

Exceptional status of MEURI: In the COVID-19 pandemic, 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 as research, they may be used ethically under the MEURI framework. Ethical use under MEURI entails adherence to the criteria listed above on justification, ethical and regulatory oversight, informed consent, and contribution to the production of evidence. Interventions offered as MEURI should not divert attention or resources from the clinical trials that need to be conducted in the country. Interventions should be offered under MEURI for a limited timeframe and be transitioned to clinical trials as soon as it is possible.

Strengthening of ethical and regulatory oversight: Health authorities (NRAs or other relevant health authorities) and RECs should become empowered on the MEURI framework and advance coordination to promote an adequate oversight in timeframes that are responsive to the pandemic.

Community engagement: The relevant health authority should assume a proactive attitude with respect to communicating to the general population about the importance of using interventions that are supported by scientific evidence or, alternatively, on the need to evaluate interventions as part of research studies with adequate safeguards, along with the risks of unproven interventions. In the exceptional cases in which MEURI is used, communication efforts should specify that the interventions have not been proven, promote an open dialogue about their risks and potential benefits, and inform about ongoing oversight.

Distinctive registry of interventions offered as MEURI: In order to ensure clarity about which unproven interventions are offered as part of research and which are offered as MEURI during

the pandemic, it is key that the latter be registered as well. All clinical trial registries –WHO’s International Clinical Trials Registry Platform ([ICTRP](#)), registries that feed that platform and national registries that do not— must allow distinguishing between protocols of clinical trials (or research in general) and MEURI protocols.

Operational recommendations for the implementation of the MEURI framework

Scientific basis: A scientific committee must have recommended the intervention proposed under MEURI on the basis of the most updated evidence. The committee can be local or international, such as boards of scientific societies or other scientific advisory committees providing advice during the pandemic. Given the global nature of the COVID-19 pandemic, recommendations issued by PAHO or WHO can also be used for this purpose (2).

Development of the MEURI protocol: The intervention must be proposed as a protocol that, at the minimum, must include the following:

- a) background,
- b) scientific justification on the basis of the recommendations of a scientific committee,
- c) objectives,
- d) population to be offered the intervention,
- e) risks and potential benefits,
- f) scientific data to be collected that may provide information on the intervention’s safety and efficacy,
- g) plan to offer the intervention to patients,
- h) informed consent documents and details about the process,
- i) data sharing plan,
- j) measures to protect confidentiality.

The protocol must also indicate the planned timeframe for offering the intervention under MEURI and presenting it to be evaluated as part of a research protocol (ideally a randomized clinical trial).

REC review and oversight: Even though an intervention offered as MEURI is not research, given its similarities with research in terms of the way it is presented and justified, along with the evaluations that are needed, RECs are best suited to assess that the wellbeing and integrity of patients receiving the intervention are protected.

Health authority involvement: The NRA (or other relevant health authorities) need to know which interventions are being offered in the country under MEURI. They have to evaluate and authorize them prior to their initiation. Health authorities are recommended to collaborate on the development of the MEURI protocol to ensure the quality and usefulness of the data that will be collected. They should also:

- Maintain a record of the interventions offered under MEURI in the country.

- Determine the timeframe to reassess the scientific evidence that justifies offering the intervention under MEURI.
- Establish the mechanisms and procedures to present the data collected as part of the MEURI protocol.
- Establish the mechanisms and procedures to supervise the intervention, which entails the possibility of requesting its modification, suspension or termination.

Registry of MEURI protocol: To ensure the transparency of interventions offered under MEURI, once they are approved they must be included in registries that feed ICTRP and in any other registry that may be locally required. The title of the protocol should make it clear that the intervention is offered under MEURI.

Efficiency and coordination: For the adequate ethical and regulatory oversight of interventions offered under MEURI during the pandemic, health authorities and RECs must have rapid and efficient mechanisms to communicate and coordinate. As it has been proposed for research, it is recommended that health authorities and RECs proceed simultaneously and avoid duplicating efforts (e.g. many RECs reviewing the same protocol) (6, 7). Additionally, health authorities, RECs and health care professionals responsible for interventions offered under MEURI should work closely from the beginning.

Monitoring the intervention: The REC and the NRA (or other relevant health authority) should monitor the intervention offered under MEURI. The health care professional responsible for the MEURI protocol must reassess the intervention periodically in the light of new evidence, and report to the REC and the NRA (or other relevant health authority) in the timeframes and manner that they previously established.

What does the REC review?

- a) The proposed intervention adheres to the seven criteria for MEURI listed above.
- b) The ethical and scientific basis for the protocol, taking into account among other things the following:
 - The available scientific evidence justifies the intervention based on its risk-benefit balance.
 - The intervention is offered to the appropriate population.
 - The informed consent process is adequate and pertinent in the context of the pandemic. The consent document specifies the details about the interventions and the data that will be collected, along with the risks and potential benefits of the unproven intervention.
 - The confidentiality of the data is guaranteed.
 - The data to be collected are relevant to provide information on the safety and efficacy of the intervention. A procedure to share data quickly with health authorities and the national and international scientific community has been established.

What does the REC oversee?

Through the reports provided by the health care professional responsible for the intervention, the REC oversees that the intervention is still justified in light of new available evidence. The REC can require modifications in the intervention or the way it is offered, its suspension or termination.

References

- (1) Pan American Health Organization. Ethics guidance on issues raised by the novel coronavirus disease (COVID-19) pandemic. Washington, DC: PAHO; 2020. Available from <https://iris.paho.org/handle/10665.2/52091>.
- (2) Pan American Health Organization. Safety of COVID-19 patients and use of medicines without scientific evidence of their benefit. Washington, DC: PAHO; 2020. Available from: <https://iris.paho.org/handle/10665.2/52256>.
- (3) Pan American Health Organization. Considerations for regulatory oversight of clinical trials in the COVID-19 pandemic. Washington, DC: PAHO; 2020. Available from: <https://iris.paho.org/handle/10665.2/52266>
- (4) World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Geneva: WHO; 2020. Available from: <https://apps.who.int/iris/bitstream/handle/10665/331446/WHO-2019-nCoV-clinical-2020.4-eng.pdf?sequence=1&isAllowed=y>.
- (5) World Health Organization. Guidance for managing ethical issues in infectious disease outbreaks. Geneva: WHO; 2016. Available from: <https://apps.who.int/iris/handle/10665/250580>.
- (6) Pan American Health Organization. Guidance and strategies to streamline ethics review and oversight of COVID-19 related research. Washington, DC: PAHO; 2020. Available from: <https://iris.paho.org/handle/10665.2/52089>.
- (7) Pan American Health Organization. Template and operational guidance for the ethics review and oversight of COVID-19-related research. Washington, DC: PAHO; 2020. Available from: <https://iris.paho.org/handle/10665.2/52086>.

Acknowledgments

This document was developed by Carla Saenz (Regional Program on Bioethics, HSS/PAHO), Sarah Carracedo (National Institute of Health, Peru) and Ana Palmero (Ministry of Health, Argentina). The following PAHO staff contributed valuably to its development, strengthening it with their contributions to discussions and their reviews to previous versions: Mauricio Beltrán, José Luis Castro, Fernanda Lessa, María Luz Pombo, Charles Preston (HSS/MT) and Ludovic Reveiz (EIH). The document benefitted from preliminary discussions with Voo Teck Chuan Voo (Centre for Biomedical Ethics, Yong Loo Lin School of Medicine, National University of Singapore; WHO Collaborating Center for bioethics) and Ignacio Mastroleo (Programa de Bioética FLACSO-Argentina, PAHO/WHO Collaborating Center for bioethics), and from the review of Hans Vásquez (Peru) and Juan Pablo Beca (Centro de Bioética de la Facultad de Medicina de la Clínica Alemana – Universidad del Desarrollo de Chile, PAHO/WHO Collaborating Center for bioethics).

This work was funded by the Wellcome Trust.