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Acronyms and abbreviations

BCG bacilli Calmette-Guérin

EUL emergency use listing

EVD Ebola virus disease

MEURI monitored emergency use of unregistered and experimental interventions

PAHO Pan American Health Organization

PHEIC public health emergency of international concern

RCT randomized controlled trial

REC research ethics committee

Glossary

Below is a glossary of terms ordered according to the order of a conceptual analysis of the designation “emergency use of unproven clinical interventions outside clinical trials contexts”.

Emergency use (use during a public health emergency): In this document, “emergency use” is shorthand for “use during public health emergencies”. It is important not to confuse a *public health emergency* with *emergency care*¹, which may be provided during or outside a public health emergency, nor with a *state of emergency* declared and lifted by a competent authority, such as a public health emergency of public health concern (PHEIC) by WHO or a national or local public health emergency by a competent local authority.

Intervention (general definition): The terms “intervention” and “use of an intervention” refer to a specific action in a biomedical setting, including clinical care, research and public health. It is better defined as “intervention ensemble”.

Intervention ensemble (technical definition): Although we define interventions as specific actions in a biomedical setting, they are usually identified with their most noticeable material, such as drugs, biologicals (e.g. antibodies, vaccines), devices, procedures and behaviour. What truly identifies an intervention, however, is how a material is used. Hence, an aspirin taken for a headache and an aspirin taken to prevent a heart attack involve the same material but are used in two different interventions. Consequently, an intervention could be defined as a coordinated set of *materials*, *operative dimensions* (e.g. dose, schedule, route of administration, risk mitigation, end-point, duration, co-interventions) and *constraints* (e.g. target populations, contraindications, likely side-effects) (2). The term “intervention ensemble” – a set of coordinated materials, operative dimensions and constraints – is a reminder that an intervention has many dimensions other than its materials (2). This definition is also useful from a regulatory point of view (3, 4).

Clinical intervention (use and regulation): In this document, “clinical intervention” refers to the use or regulation by health-care workers and/or relevant national health authorities of an intervention intended to provide a clinical benefit. The term “clinical benefit” is typically used as a synonym for the well-being or best interests of the recipients of an intervention (5). Nevertheless, use of clinical interventions has other consequences for public health and society and can benefit or harm populations. Hence, an adequate ethical evaluation of and justification for the use and regulation of clinical interventions must be broader than clinical benefit (4, 6). This document is based on a broader public health ethics evaluation of clinical interventions.

Research intervention: Clinical interventions should be distinguished from research interventions, which are use of an intervention primarily to generate knowledge for the public good (7). The fundamental distinction in ethics between clinical and research interventions is their primary aim or goal, sometimes referred to as their “intention”, and not the material aspect of the intervention nor the preliminary support for scientific evidence of their use based on a favourable risk–benefit ratio. The aim or intention of any medical activity may be evaluated in the plan or written protocol for such activities.

Unproven intervention, completely unproven intervention, “off label” use (risk-benefit umbrella terms): In this document, the term “unproven intervention” is defined as an intervention for which there is insufficient evidence of safety and/or efficacy for regular use in a health system. We also distinguish sub-groups of unproven interventions: “off-label” use, i.e. unproven modes of use of a proven intervention, and “completely unproven

¹ WHO defines emergency care as “an integrated platform to deliver time-sensitive health care services for acute illness and injury across the life course” (1).

interventions”, i.e. interventions for which there is no proven mode of use.² Alternative definitions of “off-label” use are “use of licensed medicines for indications that have not been approved by a national medicines regulatory authority” (9) and “use of a pharmaceutical agent for an unapproved indication or in an unapproved age group, different dosage, duration or route of administration” (10). The terms “unproven intervention”, “off-label” intervention” and “completely unproven intervention” are umbrella terms that group a wide variety of unproven interventions with disparate preliminary evidence and risk–benefit profiles.

Other terms for unproven intervention: Other terms often used to refer to unproven interventions or sub-groups of unproven interventions in both ethics and regulatory documents are:

- *Lack of sufficient evidence.* This first group of terms refers to or implies lack of sufficient evidence for regular use of an intervention and includes the terms “unproven”, “experimental”, “investigational”, “empirical”, “untested”, “unvalidated” and “non-validated”.
- *Lack of full authorization.* A second group of terms refers to lack of full authorization by a relevant regulatory authority for regular use in a health system, such as “unregistered”, “unlicensed”, “unauthorized” and “unapproved”.
 - *Preauthorized.* An important subgroup is preauthorized interventions, which have some form of partial authorization but have not been fully authorized.
 - *Unauthorized modes of use.* Another subgroup are unauthorized modes of use of authorized interventions, such as “off-label”, “used in unapproved ways”, “repositioned” and “repurposed” (also known as “repositioning”, “reprofiling”, “redirecting” or “rediscovering”) (11).
- *Novelty.* A third group of terms associates unproven interventions with their novelty, such as “innovation”, “innovative”, “novel”, “new non-validated” and “emergent”.
- *Desperate situation.* A fourth group of terms refers to the desperate situations in which unproven interventions are often used, such as “compassionate use”, “last chance”, “last ditch” and “rescue”.

The attributes of evidence, authorization, novelty and desperate situation are not logically equivalent, i.e. not all unproven interventions are unauthorized, novel or used in desperate situations. The same is true for the other possible combinations of attributes.

Monitored emergency use of unregistered and experimental interventions (MEURI), monitored emergency use, emergency use outside clinical trials (designations): In this document, these terms are used synonymously. They refer to a special purpose for using unproven interventions under the ethical criteria in the MEURI framework. Table 1 is a non-systematic list of WHO emergency use designations, ordered by year, that are associated with the monitored emergency use designation. Below, we also discuss the origin and use of the term MEURI and the reasons for avoiding the designation “compassionate use”.

² inspired by Aronson and Ferner (8).

Table 1. Alternative designations of MEURI

Term	Reference	Public health emergency
compassionate use (access to unapproved drug outside a clinical trial)	12	Outbreak of Ebola virus disease (EVD) in West Africa
use of unregistered interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans	12	
use of unregistered interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans	12	
use of unregistered interventions that have shown promising results in the laboratory and in animal models but have unknown adverse effects in humans	12	
use of unregistered interventions	12, 13	
MEURI	14	
compassionate use	15	
emergency use	15	
emergency or compassionate use of unproven interventions	15	
potential therapies and vaccines	15	
use of a drug outside a clinical trial	15	
emergency use of unproven interventions outside research	16	
experimental interventions used on an emergency basis outside clinical trials	16	
unproven interventions outside clinical trials during infectious disease outbreaks	16	
emergency use outside clinical trials	17	
MEURI	16	Outbreak of EVD in the Democratic Republic of the Congo
expanded access or compassionate use framework	18	
expanded access framework, with informed consent and in compliance with good clinical practice	19	
MEURI	21, 21	COVID-19 pandemic
experimental interventions on an emergency basis outside clinical trials	9	
emergency use of unproven interventions outside research	22	
MEURI	22	

Origin and use of the term MEURI: In 2014, during the outbreak of EVD in West Africa, WHO coined the ethical term MEURI (14) to avoid using the misleading “compassionate use” designation, which, in certain jurisdictions, may not comply with all the appropriate ethical criteria for use of unproven clinical interventions outside clinical trials in the MEURI ethical framework – in particular monitoring of safety and contribution to evidence (23). In previous WHO documents, the term “MEURI” also referred to: the ethical framework, i.e. the set of ethical criteria, for permissible use of unproven interventions outside clinical trials issued by WHO; non-clinical trial activities that may or may not comply with the criteria of the ethical framework; and the protocols of such activities. To avoid confusion, in this document, we mainly retain the first use (the MEURI ethical framework) and avoid expressing MEURI as an activity (emergency use outside clinical trials) and as a protocol (monitored emergency protocol).

Reasons for avoiding the “compassionate use” designation: The term “compassionate use” has many meanings and no established definition or set of ethical criteria. A possible definition could be “use of an unproven treatment outside of a clinical trial, that is usually being evaluated in clinical trials, for the clinical

benefit of an individual with a serious or life-threatening disease or condition, and no other reasonable alternatives”³. An alternative definition is “use of an investigational intervention for patients outside of an ongoing clinical trial” (14).

The pre-MEURI ethical framework for use of unproven interventions outside clinical trials used during the EVD epidemic in West Africa contained the term “compassionate use” (see Annex 1). This was later changed to MEURI. There are several reasons for not using the term “compassionate use” (24). First, “compassionate use” is strongly associated with a narrow scope of unproven interventions, such as therapeutic use in an individual in a desperate situation, of interventions that are usually being evaluated in clinical trials and hence with some evidence of safety in humans. “MEURI”, “monitored emergency use” or “emergency use outside clinical trials” is broader, including use of both therapeutic and preventive interventions at various stages of a serious disease or condition for individuals or populations, with human or non-human data that provides preliminary support. Secondly, the “compassionate use” designation is used in regulatory and non-regulatory contexts but with no universal agreement or harmonization of criteria. MEURI or emergency use outside clinical trials designates the use of unproven clinical interventions in public health emergencies, and the MEURI ethical framework proposes authoritative ethical criteria for their use. Thirdly, the term “compassionate use” has both positive and negative emotional associations that may influence its ethical justification and permissibility in particular cases. Terms such as “MEURI”, “monitored emergency use”, “emergency use outside clinical trials” and “non-trial pre-approval access” are more neutral (25).

Outside clinical trials (or other research to evaluate causal effects): In this document, “outside clinical trials” is shorthand for use of unproven interventions in activities other than randomized controlled clinical trials (RCTs) or other research to evaluate the causal effects of such interventions. We restrict the term “clinical trials” in our definition to research designs for evaluating causal effects, because national regulatory authorities generally consider this type of research, in conjunction with other relevant biomedical evidence, sufficient evidence of the safety and efficacy of unproven interventions to give authorization for regular use in their health systems.

Other terms

Ethical duty of care: “Duty of care” in this document refers to the ethical and professional obligation of health-care workers to provide care to individuals who are ill and seeking assistance. It requires that they apply their knowledge and skills for the benefit or best interests of their patient and also to explicitly acknowledge uncertainties about the risks and potential benefits of unproven interventions.

Ethical duty to conduct research: Public health emergencies, such as outbreaks, often trigger an ethical duty to conduct rigorous research rapidly. The aim of such research should be to evaluate which unproven interventions, including “off-label” use, are safe and effective for treating or preventing a disease or condition associated with the public health emergency and also to avoid diffusion of unproven interventions that are unsafe or ineffective.⁴ “Duty to conduct research” in this document refers to the ethical obligation of Member States and others with the appropriate capacity to generate sufficient scientific evidence in RCTs or other types of research to make decisions about health. Intentional generation of scientific evidence is logically in contrast to obtaining evidence by accident or not generating any evidence. The medical literature proposes various ways of implementing and integrating the duty of care and the duty to conduct research during a public health emergency (26).

³ This definition is inspired by Upshur (24).

⁴ Alternatively, this can be formulated with the negative part first and then the positive, depending on the context: “The primary aim of such ethically mandatory research should be to avoid the diffusion of unsafe and/or ineffective unproven interventions, including “off-label” use of proven interventions, to treat or prevent a disease or condition associated with the public health emergency and also to evaluate which unproven interventions are safe and effective”.

Good manufacturing practice, also referred to as “current good manufacturing practice”: The aspect of quality assurance that ensures that medicinal products are consistently produced and controlled to the standards appropriate for their intended use and as required by the product specification. Good manufacturing practice defines measures to ensure both the quality of production and quality control; to ensure that the processes necessary for production and testing are clearly defined, validated, reviewed and documented; and that the personnel, premises and materials are suitable for the production of pharmaceuticals and biologicals, including vaccines. Good manufacturing practice also has legal components, which cover responsibility for distribution, contract manufacturing and testing and responses to product defects and complaints (27).

National regulatory authority: National regulatory agencies responsible for ensuring that products released for public distribution (usually pharmaceuticals and biologicals, such as vaccines) are evaluated properly and meet international standards of quality, efficacy and safety (28).

National disaster management agency: Many countries have an established national disaster management agency or equivalent to oversee the management and coordination of emergency and disaster risk management for large-scale emergencies and disasters due to hazards. Other agencies may be assigned specific types of hazardous events, such as outbreaks or chemical and radiological nuclear events. The national disaster management agency should ensure that health is integrated into all relevant policies and plans, that health outcomes are prioritized and that health authorities participate in all related activities (28).

Pre-approval access: An alternative term for pre-authorized access to unproven interventions that have not been authorized for regular use in health care by a national regulatory authority.⁵ The term is useful for describing regulatory pathways in a neutral, general way and avoiding value-laden terms (25). For example, “compassionate use”, “expanded access programme”, “emergency use programme” or “emergency use authorization” generally refer to non-trial pre-approval access to unproven interventions for the benefit of individuals or groups that differ according to the regulations of the jurisdiction.

R&D blueprint: The WHO R&D Blueprint (30) is a global strategy and preparedness plan, approved at the World Health Assembly in May 2016, that allows rapid activation of research and development during epidemics. Its aim is to fast-track effective tests, vaccines and medicines that can save lives and avert widescale crises. The broad global coalition of experts who contributed to the Blueprint had medical, scientific and regulatory backgrounds.

⁵ This departs slightly from the definition of the Working Group on Compassionate Use and Preapproval Access (29).

Executive summary

Prevention and management of public health emergencies often trigger the ethical duty to conduct rigorous research rapidly. The primary aim of such research should be, on the one hand, to evaluate which unproven interventions – including “off-label” interventions – are safe and effective for treating or preventing a disease or condition associated with the public health emergency and, on the other, to avoid diffusion of unproven interventions that are unsafe or ineffective.

In exceptional circumstances, emergency use of interventions for which there is insufficient evidence of safety or efficacy for regular use in health systems is ethically permissible outside clinical trials or other research contexts, if the primary aim is clinical benefit for individual people or groups or benefit for populations, and if such use during public health emergencies complies with a sound ethical framework that ensures adequate justification, ethical and regulatory oversight, consent process and contribution to evidence.

During the outbreak of Ebola virus disease (EBV) in West Africa in 2014, WHO issued a framework for the ethical permissibility of use of unproven interventions outside clinical trials during public health emergencies. This framework, “monitored emergency use of unregistered and experimental interventions” (MEURI), known as “the MEURI ethical framework”, avoids the common yet misleading designation of “compassionate use”, which is associated with too narrow a scope of unproven interventions and is not based on harmonized ethical and regulatory criteria (see glossary, Reasons for avoiding the “compassionate use” designation).

Emergency use of unproven clinical interventions outside clinical trials – including “off-label” interventions – has surged during the COVID-19 pandemic, with unjustified, unconstrained use of unproven interventions, which raises serious ethical concerns. This document is intended to provide a reminder and an updated version of the ethical framework for emergency use of unproven clinical interventions outside clinical trials, the MEURI ethical framework, which is a collaborative project of WHO that began in 2014 and a normative product of WHO for its Member States.

Overview of the document

This document is divided into four sections and two annexes. **Section 1** presents a brief introduction on the duty to conduct research and the exceptional use of unproven interventions outside clinical trials during public health emergencies. It also provides a public health ethics-based justification for emergency use outside research. Finally, it explains the intended scope of the document, namely, the use of unproven drugs and biologicals for therapeutic or preventive purposes, including “off-label” uses, during public health emergencies and comments on the special cases of emergency use of vaccines outside clinical trials, preventive and therapeutic unproven interventions other than drugs and biologicals, and diagnostic unproven interventions.

Section 2 introduces a revised version of the MEURI ethical framework, summarized in Table 2, that explains the basic requirements for permissible emergency use outside clinical trials: adequate justification, ethical and regulatory oversight, consent process and contribution to evidence (“four ethical categories”, originally devised by PAHO during the COVID-19 pandemic), that are broken down into twelve ethical criteria, compiled from previous ethical guidance devised by WHO and reformulated for the present document.

Table 2. Outline of WHO’s updated ethical framework for emergency use of unproven clinical interventions outside clinical trials (the MEURI ethical framework)

I. Justification	II. Ethical and regulatory oversight
1. Public health emergency	6. Review and approval by authority and ethics committee
2. Absence of proven intervention	7. Minimization of risks
3. Impossibility of initiating research immediately	8. Responsible transition
4. Scientific support based on a favourable risk–benefit ratio	9. Fair access to scarce unproven interventions
5. Effective use of resources	
III. Consent process	IV. Contribution to evidence
10. Individual informed consent	12. Monitoring, collecting and sharing relevant data
11. Community engagement	

Section 3 provides general and operational recommendations, originally developed by PAHO during the COVID-19 pandemic, for policy makers, national regulatory authorities, health-care workers, ethics committees and others for implementing the framework. **Section 4** presents a “Q & A” of questions that the intended readers might raise. Finally, **annex 1** gives a brief chronology of WHO’s ethical framework for emergency use of unproven interventions outside clinical trials contexts (2014-2020) and **annex 2** a brief explanation of the MEURI ethical framework for use in newsletters or other communications.

Objectives of the document

This document is intended to provide policy-makers, authorities in charge of the prevention and management of a public health emergency, such as ministries of health, national regulatory authorities and national disaster management agencies, health-care workers, ethics committees and others, with:

- an updated version of the ethical framework for use of unproven clinical interventions outside clinical trials during public health emergencies (the MEURI ethical framework),
- general and operational recommendations for implementing the framework and
- answers to questions that stakeholders may raise.

1

Introduction

1.1 Ethical duty to conduct research during public health emergencies

Outbreaks and other events that may become public health emergencies frequently face a lack of safe and effective therapeutic or preventive interventions, such as drugs specific to the pathogen or condition. WHO and its partners therefore established the “WHO R&D blueprint” in 2016 to stimulate research into diseases or conditions that pose the greatest public health risks because of their epidemic potential or for which there are no or insufficient countermeasures (31).

In response to the ethical duty to conduct research during public health emergencies (17), rapid, rigorous, simple clinical trials or other types of research (32, 33) are essential to establish the safety and efficacy of unproven interventions – including “off label” interventions (9) – and to discard those that are unsafe or ineffective to avoid their use in health systems. When a PHEIC is declared, “it is critical that the global research effort is rapid, robust, conducted at scale and coordinated across multiple countries” (33).

1.2 Exceptional use of unproven interventions outside clinical trials during public health emergencies

In some public health emergencies, it may be impossible to conduct required research immediately. For example, affected areas may be overwhelmed by the emergency, be insecure or lack research capacity and infrastructure. The ethical permissibility of offering individual people, groups or populations preventive and therapeutic interventions that have not been sufficiently proven to be safe or efficacious for the disease or condition associated with the public health emergency – including “off-label” interventions – with the primary intent of benefiting them is often discussed.

Emergency use of unproven clinical interventions outside the context of clinical trials is ethically challenging for several reasons. The first is lack of sufficient safeguards. Unproven interventions are usually provided in research settings that ensure various safeguards for participants and third parties, which are not necessarily available if the interventions are provided outside the research context. The second reason is that evidence should be generated during a public health emergency, given the urgency of finding safe, efficacious interventions for diseases and conditions associated with the emergency. It would be irresponsible to miss the opportunity to learn from use of unproven interventions because they are being provided outside of clinical trials. The third reason is potential interference with scientific evaluation. While in some emergency circumstances, it may seem urgent to offer unproven interventions to individuals or groups for their potential clinical benefit, relevant research needs to be conducted to know whether such interventions are safe and efficacious. However, once unproven interventions have been widely used in the health system, it is more difficult or even impossible to initiate, conduct or complete sufficient scientific evaluation. The fourth reason is ineffective use of resources to respond to a public health emergency. Use of unsafe or ineffective unproven interventions during a public health emergency diverts health-care expertise and resources from effective clinical care and public health measures.

In response to these challenges during the outbreak of EVD in 2014, which was characterized by extremely high mortality and the absence of any proven intervention, WHO devised a list of ethical criteria for emergency use of

unproven clinical interventions outside clinical trials. The ethical term MEURI was coined to avoid the common but misleading ethical designation “compassionate use”. It may correspond to different regulatory designations or programmes of non-trial pre-approval access, such as compassionate use, expanded access and emergency use authorization, or other mechanisms that allow access to unproven clinical interventions for prevention and treatment before sufficient evidence has been attained for full approval of a national regulatory authority or its equivalent by other relevant authorities. The MEURI ethical framework was used during the outbreaks of EVD in 2014–2016 and 2018 (12, 14, 16, 20, 21). It has also been invoked since the start of the COVID-19 pandemic. In late March 2020, WHO stressed that interventions approved for other conditions and considered “off-label” should adhere to the MEURI ethical framework (9). Yet, in the absence of any proven preventive or therapeutic intervention for COVID-19, the use of unproven clinical interventions outside clinical trials (see e.g., boxes 1–3) proliferated rapidly, often failing to adhere to the MEURI ethical framework. The Pan American Health Organization (PAHO), WHO Regional Office for the Americas, issued guidance in June 2020 to clarify the MEURI framework for COVID-19 and promote its rigorous implementation during the pandemic (22).

Box 1. Convalescent plasma for COVID-19: permissible in clinical trials and monitored emergency use. *An example of a therapeutic unproven intervention that WHO considered ethically permissible for clinical trials and monitored emergency use (34)⁶*

WHO recognizes COVID-19 convalescent plasma as an experimental therapy that is appropriate for evaluation in clinical studies or as a starting material for the manufacture of experimental hyper-immune immunoglobulins. This position is based on an assessment that the potential benefit of providing antibodies that may neutralize the infectivity of SARS-CoV-2 outweighs the risks of administration of these plasma products. Reports of an RCT and several uncontrolled case series of use of COVID-19 convalescent plasma have suggested favourable patient outcomes [...]. Further clinical evidence is needed before guidance can be provided on its clinical use. WHO recommends strongly that [1] COVID-19 convalescent plasma should be used in RCTs as the most effective and efficient strategy to determine the efficacy and safety of this experimental therapy. [2] In settings where randomization of patients is infeasible, structured observational studies linked to RCTs can be considered, in which standardized protocols consistent with the active arm of an established RCT are used to generate data on the properties of the administered COVID-19 convalescent plasma, the characteristics of treated patients and pre-defined patient outcomes. [3] Where structured clinical studies are also not possible, efforts nevertheless should be made to document patient outcomes and to obtain and archive blood samples from donors and recipients for future scientific study. Data on product preparation and use collected through close cooperation between treating physicians and blood establishments and reported to a central national authority can provide information that complements the findings of RCTs. [4] COVID-19 convalescent plasma can be made available on an experimental basis through local production, provided that medical, legal and ethical safeguards are in place both for the donors of COVID-19 convalescent plasma and the patients who receive it. Detailed risk assessment must always be conducted to ensure that the blood service has sufficient capability to safely collect, process and store these specific blood components in a quality-assured manner in compliance with established standards and requirements for plasma for transfusion. WHO has previously released interim guidance for the use of convalescent plasma collected from patients recovered from Ebola virus disease [which refers to the MEURI ethical framework, see (35)]. Additionally, the WHO Blood Regulators Network published a position paper that provides helpful considerations on use of convalescent plasma in an epidemic of an emerging virus.

Box 2. BCG vaccine for COVID-19: not permissible for monitored emergency use. *An example of a preventive “off label” unproven intervention that WHO did not consider ethically permissible for monitored emergency use (36)⁶*

There is no evidence that the bacille Calmette-Guérin (BCG) vaccine protects people against infection with COVID-19 virus. Two clinical trials addressing this question are under way, and WHO will evaluate the evidence when it becomes available. In the absence of evidence, WHO does not recommend BCG vaccination for the prevention of COVID-19. WHO continues to recommend neonatal BCG vaccination in countries or settings with a high incidence of tuberculosis. There is experimental evidence from both animal and human studies that the BCG vaccine has non-specific effects on the immune system. These effects have not been well characterized, and their clinical relevance is unknown. On 11 April 2020, WHO updated its ongoing evidence review of the major scientific databases and clinical trial repositories, using Chinese, English and French search terms for “COVID-19”, “coronavirus”, “SARS-CoV-2” and “BCG”. The review yielded three preprints (manuscripts posted online before peer review), in which the authors compared the incidence of COVID-19 cases in countries where the BCG vaccine is used with that in countries where it is not used and observed that countries that routinely vaccinated neonates had fewer reported cases of COVID-19 to date. Such ecological studies are prone to significant bias from many confounders, including differences in national demographics and disease burden, testing rates for COVID-19 virus infection and the stage of the pandemic. The review also yielded two registered protocols for clinical trials, both of which are designed to study the effects of BCG vaccination given to health-care workers directly involved in the care of patients with COVID-19. BCG vaccination prevents severe forms of tuberculosis in children, and diversion of local supplies may result in neonates not being vaccinated, resulting in an increase of disease and deaths from tuberculosis. In the absence of evidence, WHO does not recommend BCG vaccination for the prevention of COVID-19. WHO continues to recommend neonatal BCG vaccination in countries or settings with a high incidence of tuberculosis.

Box 3. Chlorine dioxide for COVID-19: not permissible for monitored emergency use. *An example of an unproven intervention that WHO did not consider ethically permissible for preventive or therapeutic monitored emergency use (37)⁶*

- PAHO does not recommend oral or parenteral use of chlorine dioxide or sodium chlorite-based products for patients with suspected or diagnosed COVID-19 or for anyone else. There is no evidence of their effectiveness, and the ingestion or inhalation of such products could have serious adverse effects.
- People's safety should be the main objective of any health decision or intervention.
- PAHO recommends strengthened reporting to the national drug regulatory authority or to the office of the ministry of health responsible for drug regulation in the event of any adverse event linked to use of these products. PAHO also recommends that products containing chlorine dioxide, chlorine derivatives or any other substance presented as a treatment for COVID-19 be reported.
- Health authorities should monitor media marketing of products claiming to be therapies for COVID-19 in order to take the appropriate action.

1.3 Public health ethics justification of emergency use of unproven interventions outside clinical trials

There is no explicit justification of emergency use of unproven interventions outside clinical trials, including “off-label interventions”, based on public health ethics considerations in previous MEURI ethical guidelines. They justify it only on the basis of ethical considerations of respect for patient autonomy and beneficence, which in itself is an incomplete ethical justification for such uses.⁷ In turn, this shortcoming has been compounded by too narrow an interpretation of such ethical considerations during the COVID-19 pandemic (4, 6).

A public health ethics-based justification takes into consideration individual health needs, individual autonomy and beneficence in the context of an existential threat to humanity or large populations that can be effectively prevented or managed only by collective action – i.e. coordination, cooperation and collaboration – and other fundamental ethical considerations, such as justice, non-maleficence, equity, protection of the vulnerable and avoiding exploitation (both financial and of hope) (38). All these public health ethics considerations justify monitored emergency use outside clinical trials, including the restrictions present in the MEURI ethical framework (see section 2) and the prohibition of monitored emergency use altogether where permissibility conditions are not met (see Boxes 2-3 above).

One argument for ethical and regulatory oversight of emergency use outside clinical trials is the importance of collective action to avoid known, foreseeable harm to public health. Thus, unregulated or underregulated use of unproven clinical interventions outside clinical trials – in which individuals maximize their chances of accessing such interventions – typically interferes with the initiation, conduct or completion of the research necessary to sufficiently validate the safety and/or efficacy of unproven clinical interventions against a serious or life-threatening disease associated with a public health emergency. This situation prevents populations from achieving the public good of such research in term of knowledge and validated interventions and at the same time threatens effective management and resolution of the emergency. Moreover, it may also lead to other harm, including diffusion of unsafe or ineffective unproven clinical interventions, unnecessary stockpiling, shortages of approved medicines to treat other diseases and exploitation. Consequently, adequate ethical and

⁶ This is not necessarily the final WHO guidance on the topic. The text is taken from the recommendations of PAHO, WHO Regional Office for the Americas, with a minor edit and notes have been removed.

⁷ “**Ethical basis for MEURI** – MEURI is justified by the ethical principle of respect for patient autonomy – i.e. the right of individuals to make their own risk–benefit assessments in light of their personal values, goals and health conditions. It is also supported by the principle of beneficence – providing patients with available and reasonable opportunities to improve their condition, including measures that can plausibly mitigate extreme suffering and enhance survival” (16).

regulatory oversight of emergency use of unproven clinical interventions outside clinical trials is necessary to avoid such harm to public health while ensuring exceptional use.

WHO recognizes that Member States and the international community have the ethical obligation to ensure that national public health laws assign sufficient responsibility and power to relevant health authorities, such as ministries of health, national regulatory authorities and national disaster management agencies, for the prevention and management of public health emergencies (16, 28). Lack or inadequate regulation of both research during public health emergencies and monitored emergency use outside clinical trials breach this ethical obligation.

Ethical and regulatory oversight of emergency use of unproven clinical interventions outside clinical trials should be regarded by health-care workers and relevant health-care authorities as a public health intervention in itself to avoid harm to public health, which requires a sufficiently clear legal basis for government action, and also a system for oversight and review (see also section 3).⁸

1.4 Intended scope of the framework and unproven interventions

In this document, emergency use designation and protocols are ethically justifiable only in relation to a state of emergency declared by a competent authority and only for unproven interventions relating to the emergency (general scope of the framework). In that range, the intended scope of unproven interventions to which our ethical guidance is best adapted is the subgroup of unproven drugs and biologicals that could be used for therapeutic or preventive purposes during a public health emergency. In accordance with the most recent ethics guidelines from WHO (9, 22), we include both completely unproven interventions (interventions with no proven mode of use) and “off-label” uses (unproven modes of use of proven interventions).⁹ Our framework categorically prohibits use of harmful unproven interventions, that is, unproven interventions that are unsafe or ineffective and have a negative risk–benefit ratio for the proposed indication. Examples of such interventions during the recent COVID-19 pandemic include ingesting methanol or chlorine dioxide (industrial bleach) to prevent or treat COVID-19 (39, 40). Given that the universe of unproven interventions is beyond the intended scope, we have made some clarification of the most important ones.

Note on emergency use of vaccines outside clinical trials. It is important to distinguish the ethics of emergency mass vaccination from other non-massive emergency uses of preventive unproven interventions outside clinical trials (e.g. pre- and post-prophylaxis prevention strategies, ring vaccination) because of the different impacts on public health and well-being (18). The Working Group considered that ethical guidelines for mass emergency use of novel vaccines for a disease or condition associated with a public health emergency (e.g. novel vaccines for COVID-19) should be addressed in a separate document or documents, given its distinct impact on public health and well-being. The MEURI ethical framework may prove useful for emergency use of such interventions, but it should be adapted to the relevant ethical and regulatory considerations (41–45).

Note on preventive and therapeutic unproven interventions other than drugs and biologicals. We recognize that similar ethical problems may be associated with emergency use of devices, clinical procedures and other

⁸ “Ensuring the sufficiency of national public health laws — As discussed later in this document, certain public health interventions that might be necessary during an infectious disease outbreak (e.g. restrictions on freedom of movement) depend on having a clear legal basis for government action, as well as a system in place to provide oversight and review. All countries should review their public health laws to ensure that they give the government sufficient authority to respond effectively to an epidemic while also providing individuals with appropriate human rights protections.” (16).

⁹ This distinction is inspired by a similar one, “completely unauthorized” and “unauthorized modes of use”, by Aronson & Ferner (8).

interventions. The usefulness of the MEURI framework may depend on whether special ethical and regulatory considerations are necessary for such interventions. For example, the requirement of good manufacturing practice does not apply to procedures such as pronation, but analogous quality standards for clinical procedures or other types of unproven clinical interventions should be considered.

Note on diagnostic unproven interventions. The WHO emergency use listing (EUL) and several national regulations on medical countermeasures for public health emergencies include unproven interventions for diagnostic purposes (43, 46). The MEURI ethical framework does not include such interventions so far, and its application to them may require special ethical and regulatory considerations.

Outline of the scope of the framework. Below, we illustrate the scope of the framework and of the intended interventions with simplified examples of unproven clinical interventions proposed during the COVID-19 pandemic. These examples are sensitive to time, the stage of the disease (mild, moderate, severe, critical), the target population and other variables. We present examples of unproven clinical interventions for COVID-19 at the beginning of the pandemic, for at least one stage of the disease and one relevant target population group. Cells that are fully crossed represent categories of interventions that fall outside the intended scope of the framework. Cells that are crossed with dashed lines represent interventions that might require special ethical considerations (see notes above). Given the inherent limits of any ethical framework, all applications to specific cases or interventions may require further ethical consideration.

Type of emergency use	
Use during a public health emergency declared by a competent authority (primarily PHEIC, but may also be applied in a national or local public health emergency)	Emergency care for an individual or group outside a public health emergency

Illustrative examples of materials for unproven interventions for COVID-19				
Drugs	Biologicals	Medical devices	Procedures	Others
Hydroxychloroquine	BCG vaccine	Oxygen helmet	Pronation	Oxygenation-targets
Ivermectin	Convalescent plasma	Cannulae	Fluid strategies	Stem-cell therapy

Illustrative examples of purpose and type of unproven interventions for COVID-19				
Therapeutic		Preventive		Diagnostic
"Off label" use (unproven modes of use of proven interventions)	Completely unproven interventions	"Off label" use (unproven modes of use of proven interventions)	Completely unproven interventions	
Hydroxychloroquine (proven use: malaria)	Remdesivir	Hydroxychloroquine (proven use: malaria)	Pre- and post-prophylaxis strategies	
Ivermectin (proven use: intestinal conditions caused by parasitic worm)	Novel monoclonal antibodies	BCG vaccine (proven use: neonatal vaccination in settings with a high incidence of tuberculosis) (36)	Mass vaccination	

Illustrative examples of harmful unproven interventions for COVID-19 (prohibited in the MEURI ethical framework)
Chlorine dioxide (therapeutic and preventive use)
Methanol (therapeutic and preventive use)

2

**An ethical framework for
emergency use of unproven
clinical interventions outside
clinical trials**

2.1 Introduction

The main aim of the MEURI ethical framework is to answer the fundamental question of when, if ever, it is ethically permissible to use unproven clinical interventions outside clinical trials during a public health emergency. On a strictly exceptional basis it may be ethically permissible to use an unproven intervention outside clinical trials for the clinical benefit of individual people or groups or to benefit populations if the monitored emergency use meets the rigorous ethical criteria spelled out by the MEURI ethical framework.

WHO's revised MEURI framework builds on the four categories of ethical criteria devised by PAHO: justification, ethical and regulatory oversight, consent process and contribution to the generation of evidence (22). These categories are further broken down into twelve ethical criteria stated in previous versions of the MEURI framework. The explanation of each criterion is supplemented by general comments. General and operational recommendations for implementation of this framework are presented in section 3.

2.2 Outline of the MEURI ethical framework

WHO's ethical framework for emergency use of unproven clinical interventions outside clinical trials (the MEURI ethical framework)	
I. Justification	II. Ethical and regulatory oversight
1. Public health emergency	6. Review and approval by authority and ethics committee
2. Absence of proven intervention	7. Minimization of risks
3. Impossibility of initiating research immediately	8. Responsible transition
4. Scientific support based on a favourable risk–benefit analysis	9. Fair access to scarce unproven interventions
5. Effective use of resources	
III. Consent process	IV. Contribution to evidence
10. Individual informed consent	12. Monitoring, collecting and sharing relevant data
11. Community engagement	

2.3 Justification

Summary of ethical criteria

1. Public health emergency	This ethical framework was developed for PHEICs declared by WHO. It may be also useful for Member States in managing non-international public health emergencies, always in compliance with their legal framework.
2. Absence of proven interventions	A national regulatory authority or other relevant authority should determine that there are no proven efficacious or safe clinical interventions or that those available are not satisfactory.
3. Impossibility of initiating research immediately	A national regulatory authority or other relevant authority determines that it is not possible to initiate research on a given intervention for a disease or condition associated with the public health emergency immediately.
4. Scientific support based on favourable risk–benefit analysis	A national regulatory authority or other relevant authority through a qualified scientific advisory committee determines that (4.1.) scientific data are available, at least from laboratory or animal studies, that provide preliminary support for the efficacy and safety of an unproven intervention, and that (4.2) use of unproven clinical interventions outside clinical trials has a favourable risk–benefit analysis.
5. Effective use of resources	A ministry of health or other relevant authority in charge of prevention or management of a public health emergency should ensure that emergency use outside clinical trials does not preclude or delay necessary research on unproven interventions nor divert attention or resources from effective clinical care and/or public health measures that may be crucial.

Commentary

1. Public health emergency	This ethical framework was developed for PHEICs declared by WHO. It may be also useful for Member States in managing non-international public health emergencies, always in compliance with their legal framework.
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Public health emergency determined by a competent authority (general scope of this framework). In this framework, emergency use designation and protocols are justifiable only in relation to a state of public health emergency declared by a competent authority and only for unproven interventions related to the emergency. In the case of a PHEIC, it is the responsibility of WHO, through its Director-General, to determine the state of emergency (48). This framework may also be used by Member States to manage national public health emergencies, always in compliance with their legal framework. In that case, a national health authority or other relevant authority must determine that there is an emergency that affects, or has significant potential to affect, public health, which involves a specified pathological agent or agents and a specified serious or life-threatening disease or condition that may be attributable to such agent or agents.¹⁰

No pretexts requirement. Relevant authorities and health-care workers must not use the emergency use designation or protocols as a pretext to disguise other aims (50). For example, it must not be used as a means to circumvent ethical oversight of the use of unproven interventions in research, to bypass research regulatory restrictions seen as cumbersome or unfit, or to avoid conducting clinical trials when they are feasible (22, 51). Also, an emergency use protocol should not be seen as a means to provide the intervention more rapidly. Account must be taken of the possibility that research cannot be initiated rapidly in many parts of the world, although it is increasingly difficult to argue that it cannot be conducted at all (22). WHO has addressed the problems mentioned above in ethical guidelines on research during public health emergencies, including justification of emergency research, application of ethical standards for research during public health emergencies and rapid review of research to facilitate time-sensitive ethics review (52–54).

Ethical permissibility in exceptional circumstances. Emergency use of unproven clinical interventions outside clinical trials may be ethically permissible during public health emergencies in exceptional circumstances. Cases such as the West African EVD epidemic and the COVID-19 pandemic are exceptional for several reasons, including their magnitude as compared with other outbreaks, the lethality of the outbreak in whole of populations or sub-populations, their contagiousness and the burden they impose on health systems (51); however, a systematic analysis should be conducted on what constitutes “exceptional circumstances” (51).

2. Absence of proven interventions	A national regulatory authority or other relevant authority should determine that there are no proven efficacious or safe clinical interventions or that those available are not satisfactory.
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Absence of proven interventions. Because of the possibility of harm, emergency use outside clinical trials is covered by the ethics of “last resort” measures, when no other reasonable alternatives exist or are feasible (50). Therefore, use of an unproven clinical intervention would not be justifiable if a safer, more efficacious or less uncertain clinical intervention was available with a similar prospect of success.

Available proven interventions are not satisfactory. The existence of a proven clinical intervention for the disease or condition associated with a public health emergency (e.g. corticosteroids for the treatment of patients with severe and critical COVID-19) does not necessarily obviate the justification for monitored emergency use. There may still be no proven interventions for other purposes (e.g. prevention), for different stages of a disease or condition (e.g. mild, moderate), or in general when available proven interventions have not been satisfactory or successful in eradicating the disease or preventing outbreaks.

¹⁰ inspired by Project Bioshield Act (49).

3. Impossibility of initiating research immediately	A national regulatory authority or other relevant authority determines that it is not possible to initiate research immediately on a given intervention for a disease or condition associated with the public health emergency.
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Impossibility of initiating research immediately. Monitored emergency use outside clinical trials was not devised to substitute for research but as a bridge to conduct research (e.g. WHO Solidarity Trial), permit clinical use in the face of strong uncertainty and to create the conditions for collecting relevant data to understand potential benefits and harms. It is also designed to prevent unjustified, unconstrained use of unproven clinical interventions outside clinical trials (23). In public health emergencies, it may be impossible to conduct research that is urgently required immediately, such as when affected areas are overwhelmed by a peak in the emergency and lack security, resources, research capacity or research infrastructure. Impossibility of initiating research immediately as explained above is the main reason for justifying emergency use outside clinical trials in this ethical framework but does not exclude others.

Other possible reasons for emergency use outside clinical trials. Other reasons than the impossibility of initiating research immediately may justify monitored emergency use outside clinical trials. First, participation in clinical trials or other research may be infeasible for populations who live far from health research centres. Secondly, people who do not meet the inclusion criteria cannot be enrolled (55, 56). Thirdly, unproven interventions that reach a significant threshold of efficacy or safety in clinical trials or other research may be proposed for emergency use before the research is completed (42, 43). Fourthly, people may be unwilling to enrol in clinical trials or other research, although this is a particularly controversial reason (57, 58). None of the above justifies noncompliance with the core ethical considerations of justification, consent process, oversight and contribution to evidence in this framework. Ministries of health or other relevant authorities in charge of prevention and response to public health emergencies should balance these and other reasons for emergency use outside clinical trials against reasons for forbidding, limiting or accommodating such use (see also criterion 5, Effective use of resources) (16).

4. Scientific support based on a favourable risk–benefit analysis	A ministry of health, national regulatory authority or other relevant authorities through a qualified scientific advisory committee should determine that (4.1.) scientific data are available, at least from laboratory or animal studies, that provide preliminary support for the efficacy and safety of an unproven intervention, and that (4.2.) use of unproven clinical interventions outside clinical trials has a favourable risk–benefit analysis.
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Requirement for a qualified scientific committee. Ministries of health, national regulatory authorities or other authorities in charge of prevention and management of a public health emergency must conduct or adopt a scientific assessment of evidence by a qualified scientific committee for any unproven intervention proposed for emergency use outside clinical trials (see section 3.3). Unproven interventions outside clinical trials must not be used by the clinical community or by national or regional governments of Member States without such scientific assessment. Scientific assessment of the available evidence must be continuous, and decisions on emergency use should be revised in the light of new relevant evidence.

Requirement for proportionality of scientific capacity. The scientific capacity for evaluation should be proportional to the degree of uncertainty, risk and previous experience with the proposed unproven intervention (59). Greater uncertainty and risk and less experience with an unproven intervention will require scientific reviewers to have greater, more nuanced capacity for evaluating preclinical and scientific data and for conducting risk–benefit analyses, as in biomedical research (60, 61). Scientific capacity and resources for evaluation should be improved continuously and proactively, before a public health emergency. WHO must collaborate with Member States to fulfil their obligations to provide financial, technical and scientific resources for independent scientific committees, especially in low- and middle-income countries and contexts.¹¹

¹¹ “The following are key elements of the obligations of governments and the international community [...] **Providing financial, technical, and scientific assistance** — Countries that have the resources to provide foreign assistance should support global epidemic preparedness and response efforts, including research and development on diagnostics, therapeutics, and vaccines for pathogens with epidemic potential. This support should supplement ongoing efforts to build local public health capacities and strengthen primary health care systems in countries at greatest risk of harm from infectious disease outbreaks” (16).

Requirement for transparency and publication of scientific evaluations. Unproven interventions for emergency use must be selected by a qualified scientific committee in a stepwise, public, transparent manner. Scientific assessment of and justification for the selection of unproven interventions for emergency use outside clinical trials should be available to the public and to the scientific and clinical communities. Transparency and publication of scientific evaluations for monitored emergency use should be part of a broader strategy for ensuring public trust.

Requirement for preliminary scientific support based on a favourable risk–benefit analysis. The terms “unproven intervention”, “off-label’ intervention” and “completely unproven intervention” are umbrella terms that cover a variety of unproven interventions with different levels of preliminary evidence and risk–benefit profiles that should be evaluated further for ethical justification of monitored emergency use outside clinical trials. The criterion of *scientific support based on a favourable risk–benefit analysis* requires both that a candidate unproven intervention meet a sufficient threshold of evidence for monitored emergency use outside clinical trials with preliminary scientific support for safety and efficacy in at least laboratory or animal studies and a favourable risk–benefit ratio for the proposed mode of use. Based on this criterion, unproven interventions for emergency use outside clinical trials can be classified into two broad subgroups, illustrated by recent examples. More research on such cases might, however, result retrospectively in a different evaluation (e.g. hydroxychloroquine for COVID-19 may prove to belong to the first group instead of the second):

- The first subgroup is *unproven interventions without sufficient preliminary evidence and/or a negative risk–benefit analysis*. Our framework categorically prohibits the use of harmful unproven interventions, that is, unproven interventions for which there is insufficient preliminary scientific evidence, that are known to be unsafe or ineffective, or that have a negative risk–benefit analysis for the proposed indication for clinical or public health reasons. Examples of such interventions during the COVID-19 pandemic include ingesting methanol or chlorine dioxide (industrial bleach) to prevent or treat the disease (39, 40). Observational studies, post-marketing surveillance and case reports provide sufficient evidence for the harmfulness of unproven interventions, and evidence from toxicological and animal studies and other mechanistic studies may also provide evidence of potential toxicity. Evidence from clinical trials is not necessary for considering an unproven intervention harmful, as clinical or public health harm may not be detected in well-designed RCTs. Member States should be reminded of their obligation to refrain from, stop and prevent the use of harmful unproven interventions to individual people, groups or populations by all available means. Health-care workers should also do their part in this obligation, within their capacity.
- The second subgroup is *unproven interventions for which there is sufficient preliminary evidence and a favourable risk–benefit analysis*. This group consist of either “off-label” interventions (unproven modes of use of proven interventions) or completely unproven interventions associated with various levels of uncertainty and scientific evidence but which have been assessed by a qualified ethics committee as having a favourable risk–benefit analysis in a systematic approach. For example, this subgroup includes completely unproven interventions used in humans for the first time under emergency use outside clinical trials, with only laboratory or animal evidence (e.g. ZMapp for EVD at the onset of the outbreak in 2014); completely unproven interventions that have been used in humans in clinical trials or non-trial pre-approval access programmes but that have not reached the threshold of sufficient evidence for regular use in the health-care system (e.g. remdesivir for COVID-19 at the onset of the pandemic in 2020); as well as unproven modes of use of proven interventions (e.g. hydroxychloroquine for COVID-19 at the onset of the pandemic; convalescent plasma for EVD or COVID-19 at the onset of those outbreaks).

Systematic approach for assessing the risk–benefit of unproven interventions. The minimum sufficient evidence and favourable risk–benefit analysis that justifies emergency use of an unproven clinical intervention outside clinical trials is open to interpretation and reasonable disagreement in a given context. A systematic approach to risk–benefit analysis and to selection of unproven clinical interventions is considered a better approach than a

non-systematic one and should be further developed according to the available literature. For example, lessons from systematic risk–benefit evaluation of unproven interventions in emergency and non-emergency research can be applied to monitored emergency use outside clinical trials (51, 62). Appraisal of preclinical and clinical data (when available) is complex and requires the highest standards of scientific expertise, plurality of opinions and transparency in selecting evaluators (61, 62). The requirement of favourable risk-benefit analysis should not be determined from solely a technical or clinical point of view but should incorporate the broader public health ethics point of view supported by this document.

5. Effective use of resources	A ministry of health or other relevant authorities in charge of prevention or management of a public health emergency should ensure that emergency use outside clinical trials does not preclude or delay the necessary research on unproven interventions nor divert attention or resources from the provision of effective clinical care and public health measures crucial to preventing or managing the emergency.
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Requirement for effective use of resources (16, 22). Resources for a response to a public health emergency are always limited. The ministry of health or other relevant authorities in charge of prevention or management of a public health emergency should ensure that the limited resources available for research, clinical care of proven efficacy and other public health measures are not diverted to emergency use outside clinical trials or that monitored emergency use threatens or delays activities that may be crucial for an effective response to the public health emergency. Constant monitoring and adaptation of policies, regulations and decisions are necessary during the response to a public health emergency.

2.4 Ethical and regulatory oversight

Summary of ethical criteria

6. Review and approval by authority and ethics committee	The national regulatory authority or other relevant authority, through a qualified ethics committee, must review and approve emergency use of unproven clinical interventions outside clinical trials.
7. Minimization of risks	The national regulatory authority or other relevant authority should ensure that adequate resources and safeguards are available to minimize the risks posed to recipients of emergency use and to third parties. This includes creating intervention-specific risk-minimization plans and strategies. An ethics committee should evaluate whether such plans and strategies are implemented or whether other authorities have ensured adequate protection.
8. Responsible transition	National health authorities, health-care workers or others in charge of emergency use protocols should plan for responsible transition of individuals, groups or populations to research or regular health care. A preliminary plan should be presented to the appropriate authorities, evaluated by ethics committees and communicated in international registries. Ministries of health or other relevant authorities in charge of the response to the public health emergency should plan and ensure that resources and healthcare teams in charge of monitored emergency use are transferred to other useful activities for prevention and management of the public health emergency.
9. Fair access to scarce unproven interventions	The national regulatory authority or other relevant authority should establish mechanisms for deciding on allocation of scarce unproven interventions, taking into account the assessments of scientific and ethics committees.

Commentary

6. Review and approval of authority and ethics committee	The national regulatory authority or other relevant authority, through a qualified ethics committee, must review and approve emergency use of unproven clinical interventions outside clinical trials.
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Review and approval by national authority and ethics committee. Emergency use outside clinical trials requires the review, approval and monitoring of approved uses by an appropriate ethics committee and the national regulatory or other relevant authority (22).

Requirement for a qualified ethics committee. A research ethics committee (REC) or an equivalent qualified committee that meets local norms and has the capacity of evaluation for the type of proposed unproven intervention must review the protocol of monitored emergency use. While emergency use does not constitute research but rather access to an unproven intervention outside clinical trials for the benefit of its recipients or the population, it should be guided by the ethical principles that govern the use of unproven interventions. Its similarity to and relation with research justifies use of the research regulatory and review system (16, 22, 63). (See section 3.3.)

7. Minimization of risks	The national regulatory authority or other relevant authority should ensure that adequate resources and safeguards are available to minimize the risks posed to recipients of emergency use and to third parties. This includes creating intervention-specific risk-minimization plans and strategies. An ethics committee should evaluate whether such plans and strategies are implemented or whether other authorities have ensured adequate protection.
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Minimization of risks and risk-minimization plans. Administration of unproven clinical interventions necessarily involves risks, some of which will not be fully understood without research (16). The risks may affect both recipients of unproven interventions and third parties. In order to protect them appropriately, national authorities must assure that a risk management plan specific to each intervention, designed by a qualified scientific committee, is available. The plan should be concise, indicating the major potential risks and major sub-groups of recipients who should not be treated or treated with caution, what should be monitored for toxicity, when to stop the intervention for safety reasons and other aspects.

Good manufacturing practice or analogous quality standards. Only unproven clinical interventions manufactured according to good manufacturing practice should be used for monitored emergency use outside clinical trials (16). WHO devised the EUL as a complementary means for Member States, manufacturers and others to operationalize assessment of good manufacturing practice during public health emergencies (see section 4) (43, 64). Analogous quality standards should apply to unproven interventions that are not covered by good manufacturing practice.

Risks to recipients of monitored emergency use. Known risks to recipients should be minimized to the extent possible (e.g. administration under hygienic conditions; safety precautions similar to those used during research, with monitoring and access to emergency medication and equipment; and provision of necessary supportive treatment) (16).

Risks of monitored emergency use to third parties. Monitored emergency use of unproven interventions outside clinical trials may also pose risks to third parties, such as uncontrolled diffusion of unsafe or ineffective interventions (65), undue interference with research, unnecessary stockpiling and creation of shortages of proven interventions for other diseases or conditions (9). A national regulatory authority or other relevant authority should ensure that adequate policies, risk mitigation plans and other mechanisms are in place to minimize risks to third parties, and an ethics committee should evaluate whether such plans and strategies are implemented or certify that other authorities have ensured adequate protection (66). For example, mechanisms to limit the risk of uncontrolled “off-label” use can be implemented.

Mechanisms to limit the risk of uncontrolled “off-label” use. Relevant health authorities can issue executive or emergency regulations to limit the prescription of a proven or unproven intervention, such as limiting the prescription of opioids (67). Such regulations could restrict the supply of prescriptions, allow prescription only by a certain subgroup of health-care workers, monitor health-care workers’ prescription patterns or impose other administrative mechanisms of restriction to avoid the harm of unconstrained, unjustified use of unproven “off-label” interventions outside clinical trials. Such limitations should be part of a broader response to the public health emergency and include consideration of their potential negative consequences (67).

8. Responsible transition	National health authorities, health-care workers or others in charge of emergency use protocols should plan for responsible transition of individuals, groups or populations to research or regular health care. A preliminary plan should be presented to the appropriate authorities, evaluated by ethics committees and communicated in international registries. Ministries of health or other relevant authorities in charge of the response to the public health emergency should plan and ensure that resources and healthcare teams in charge of monitored emergency use are transferred to other useful activities for prevention and management of the public health emergency.
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Responsible transition plan for recipients of monitored emergency use. Unproven clinical interventions, including “off-label” interventions, should be offered under monitored emergency use protocols for a limited time to avoid diffusion of unsafe or ineffective interventions in the health system (see section 3.3) (22). Responsible transition of recipients of monitored emergency use outside clinical trials should be planned and evaluated. Responsible transition plans for recipients of monitored emergency use should include (68):

- making arrangements for after-care (e.g. referrals) or enrolment in research;
- ensuring safety;
- informing recipients about the reasons for ending monitored emergency use;
- communicating with families or other caregivers; and
- resolving any misconceptions or misunderstandings.

There are at least two stages after an emergency use protocol (post-MEURI stages): provision of effective clinical care (after-care) and enrolling individuals into clinical trials or other research that could not be initiated immediately at the start of the public health emergency. In the case of acute diseases or conditions or severe or critical stages, responsible transition of individuals might be limited or not necessary.

Responsible transition plan of resources and health teams in charge of monitored emergency use. The continuous scientific assessment of the available evidence may require stopping monitored emergency use before the termination of a PHEIC or other public health emergencies. According to the criterion of effective use of public health resources (16), ministries of health or other relevant authorities in charge of the response to the public health emergency should ensure that resources and health-care teams in charge of monitored emergency use are transferred to other activities for prevention and management of the public health emergency.

9. Fair access to scarce unproven interventions	Ministries of health or other relevant authorities should establish the mechanisms for deciding on allocation of scarce unproven interventions, taking into account the assessments of scientific and ethics committees.
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Fair access to scarce unproven interventions. Clinically unproven interventions that qualify for emergency use outside clinical trials may not meet the demand, and choices will have to be made about which individual people, groups or populations will receive each intervention, when and for what purpose. Ministries of health or other relevant authorities should establish mechanisms for making such decisions, taking into account the assessments of the scientific advisory committee and the ethics committee and the principles of fair access to scarce resources (16). The experience of established advisory committees and literature on allocative models should be taken into account in prioritizing unproven clinical interventions outside clinical trials (69–71).

No discrimination. There should be no unfair discrimination or bias towards any person or group in determining access to unproven interventions for emergency use. Authorities and health-care workers should determine access on the basis of equal concern and respect (72, 73) for potential recipients, medical need and medical suitability, and not celebrity, wealth, migration status, social media pressure, past contributions to society or other discriminatory traits, such as race, sex, language or religion, recognized in international ethical guidelines and law. The duty of non-discrimination does not preclude prioritization consistent with the relevant ethical guidelines (16).

2.5 Consent process

Summary of ethical criteria

10. Individual informed consent	A qualified ethics committee should determine that the informed consent of individuals or the appropriate, authorized representative is properly obtained.
11. Community engagement	A ministry of health or other relevant authority should establish appropriate policies for community engagement to prevent social practices that may threaten the validity of adequate consent, such as overstatement of evidence and potential benefits, understatement of risk and uncertainties, undue promotion of unproven interventions, undue influence on the public and the medical community or exploitation of vulnerability.

Commentary

10. Individual informed consent	A qualified ethics committee should determine that the informed consent of individuals or their appropriate authorized representative is properly obtained.
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Informed consent process. Obtaining informed consent is a process. It is not limited to signing a written document or suitable alternative documentation of the process. The consent process should enable informed consent of recipients of unproven clinical interventions by ensuring their decision to receive an unproven clinical intervention outside the context of a clinical trial is made voluntarily, with adequate understanding of the consequences of participation. The requirement of an informed consent process does not preclude the mandatory use of public health interventions consistent with the relevant ethical guidelines.

Individual informed consent. Potential recipients of monitored emergency use interventions outside clinical trials should decide voluntarily, on the basis of an assessment of the risks and benefits of their own situation, whether they wish to receive the unproven clinical intervention. If necessary, proxy consent should be obtained (16). For example, first-line health-care workers may assess their risks and benefits differently from someone in a less risky group. They must therefore be given the relevant information in the context of a public health emergency such as the risks and potential benefits, alternatives (e.g. proven health care, research), and informed of the insufficiently proven status and emergency nature of clinical interventions, including “off-label” uses (9, 16, 22).

Adaptation of informed consent. When necessary, authorities and health-care workers should adapt documentation of the consent process to the realities of a public health emergency (e.g. provide alternatives to written consent).

Waiver of informed consent. Health-care workers are not ethically permitted to waive individual or proxy informed consent for emergency use outside clinical trials of unproven clinical interventions.

Acknowledgment of uncertainty by the scientific community. Health-care workers may have their own opinions about whether an unproven clinical intervention is more likely to be beneficial or harmful; however, a consent process for use of unproven clinical interventions that does not explicitly recognize the scientific community’s uncertainty about the risk–benefit profile of an unproven intervention would not be ethically appropriate.

11. Community engagement	A ministry of health or other relevant authority should establish appropriate policies for community engagement to prevent social practices that threaten the validity of an adequate consent process, such as overstatement of evidence and potential benefits, understatement of risk and uncertainties, undue promotion of unproven interventions, undue influence on the public and the medical community or exploitation of vulnerability.
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Community engagement. In communications on emergency use outside clinical trials of both completely unproven or “off-label” interventions, national health authorities, health-care workers and others must refrain from overstating the evidence and potential benefits, understating the risks and uncertainties and exploiting the hope of populations for any reason, including political or economic gain (74). National health authorities and health-care workers should provide information about the uncertainties, risks and potential benefits of interventions that have not been proven safe or efficacious and promote dialogue about monitored emergency use outside clinical trials in order to avoid false perceptions of risk-benefit profile and overstatement of evidence of unproven interventions. Community engagement is essential for meaningful consent, particularly in the context of a public health emergency (22). All aspects of a public health emergency response should be supported by early, continuing engagement with the affected communities. Community engagement is essential not only because it is ethically important but also to establish and maintain trust and preserve social order¹².

Avoidance of exploitation. In outbreaks and other public health emergencies, desperate individuals or groups might be willing to try any intervention offered or promoted, regardless of the expected risks and benefits. Authorities and health-care workers have a duty not to exploit individual vulnerability¹³ by offering or promoting therapeutic or preventive interventions for which there is no reasonable basis to believe that the potential benefits outweigh the uncertainties and risks. This duty does not preclude emergency use of unproven clinical interventions outside clinical trials that complies with the current ethical framework (16).

2.6 Contribution to evidence

Ethical criteria

12. Monitoring, collecting and sharing relevant data	A national regulatory authority or other relevant authority should establish plans for monitoring emergency use of unproven interventions outside clinical trials for safety and efficacy and for collecting and sharing the results with wider medical and scientific communities and appropriate parties in a timely manner. An ethics committee should evaluate whether plans for monitoring, collecting and sharing data are in place and are implemented by the appropriate parties.
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Commentary:

Ethical duty of contribution to the generation of evidence. While the primary aim of monitored emergency use of unproven interventions outside clinical trials is clinical benefit to individual people or groups or populations, it must also contribute to generation of evidence of the risk-benefit profile of unproven interventions, including “off-label” uses, which is urgently needed in the context of public health emergencies (22). WHO and other international bodies have recognized this as an ethical duty in other guidance and related documents (see section 4, Table 3) (7, 9, 12, 16, 17, 20, 22).

Responsibility for plans to acquire relevant data. National regulatory and other authorities are responsible for drawing up plans for monitoring, collecting and sharing relevant data and determining the responsible parties. For example, private sponsors of research on unproven drugs (e.g. pharmaceutical companies, funded researchers) are also responsible for monitoring, collecting and sharing meaningful, relevant data for monitored emergency use of such interventions outside clinical trials, typically through pre-approval access programs. However, some unproven interventions that are subject to different proprietary rights (e.g. convalescent human plasma) may have public sponsors (e.g. national regulatory authority or national blood banking and transfusion authority) and healthcare teams, who should bear this responsibility. National regulatory and other

¹² In particular, Guideline 2. Involving the local community (16).

¹³ In particular, Guideline 3. Situations of particular vulnerability (16).

relevant authorities should also plan for collection and sharing of relevant data on “off-label” uses of proven interventions. Authorities should avoid placing responsibility on parties that do not have the suitable scientific, ethical or organizational capacity.

Distinct registry of monitored emergency use and avoidance of mischaracterization. Appropriate collection and sharing of data include not only sharing results but also registering emergency use protocols, including informed consent forms and other relevant material, in national and international registries and with the scientific and medical community (see sections 3.2 & 3.3). Health authorities, health-care workers, ethics committees and other stakeholders must avoid mischaracterization of emergency use outside clinical trials, including “off-label” use, as activities (e.g. “observational research”, “compassionate use”, “quality improvement”) to evade the requirements of justification, ethical and regulatory oversight, consent processes and contribution to evidence established in the MEURI ethical framework (22, 24).

Monitoring safety and signs of efficacy. National regulatory authorities and other relevant authorities and ethics committees should receive follow-up information on monitored emergency use protocols for periodic reassessment of safety or signs of efficacy from responsible health-care workers, in a time and manner established in plans for relevant data (22).

Coordination of relevant data collection and sharing. All individuals and entities involved in monitored emergency use outside clinical trials should do their part to share relevant, accurate data in a timely manner as part of the network of activities that generate data during a public health emergency (16). Coordination with national authorities is essential for identifying relevant data to be collected and shared without delay, accurately and transparently with relevant national and global stakeholders (22). Ethically appropriate, rapid sharing of data on emergency use outside clinical trials can allow those in charge of prevention and management of a public health emergency to identify unsafe or early signs of lack of effectiveness of unproven interventions and guide effective use of limited resources (16). WHO has addressed some ethical issues of data collection and sharing during public health emergencies in previous guidelines¹⁴.

Monitored emergency use protocols and aggregated evidence. It is essential to aggregate evidence from emergency use of unproven clinical interventions outside clinical trials, including “off-label” uses. Advancing its use as part of monitored emergency use protocols or programs offering pre-approval access to a large group of patients (instead of to single patients) allows efficient, systematic data collection and does not pose an undue burden on national authorities and ethics committees, which are already overstretched during public health emergencies (see section 3.3) (22).

Non-commercial use as a mechanism for contribution to evidence. A national regulatory or other relevant authority should comply with or establish sufficient safeguards to prevent fully commercial use of completely unproven interventions before their authorization for regular use, including appropriate restrictions on commercialization and promotion, to ensure sufficient incentives for research and contribution to the generation of evidence during a public health emergency (75, 76). An ethics committee should determine that non-commercial safeguards are in place when reviewing monitored emergency use protocols.

¹⁴ In particular Guidelines 5. Public Health Surveillance, 10. Rapid data sharing, 11. Long-term storage of biological specimens collected during infectious disease outbreaks (16).

3

**Implementation of the
MEURI ethical framework:
recommendations**

3.1 Introduction

The recommendations for implementation of oversight, monitoring and review of emergency use of unproven interventions outside clinical trials presented below are based on the research ethics system, for two reasons, first, because of the similarities – but not identity – with the safeguards for use of unproven interventions to acquire generalizable knowledge (unproven research interventions), and, secondly, because, in several cases, the responsibility for monitored emergency use is devolved to specific health agencies, such as national regulatory authorities (e.g. pre-approval access programmes).

Currently, many low- and middle-income countries or contexts do not have an optimally functioning research ethics system, nor adequate pre-approval access regulations and have insufficient capacity and expertise to regulate even every day, non-emergency research. Hence, a research ethics system is necessary and should be developed proactively by governments, with WHO support.

Nevertheless, not all jurisdictions rely partially or completely on research ethics oversight, monitoring and review to manage monitored emergency use of unproven clinical interventions. Instead, they rely on medical ethics oversight systems, a suitable mix between research and medical systems and even sui-generis systems designed for the purpose (e.g. regulations on medical innovation). This should not obviate adaptation and implementation of the four main ethical categories of the MEURI framework by competent authorities through appropriate coordination and with WHO. For instance, in the operational recommendations, we use REC as the default option, but ethical criteria and recommendations can be implemented by other qualified ethics committees and review systems.

The following recommendations for monitored emergency use of unproven interventions are taken, with minor revisions and adjustments, from "Emergency use of unproven interventions outside of research: ethics guidance for the COVID-19 pandemic" devised by PAHO, WHO Regional Office for the Americas (22).

3.2 General recommendations

Exceptional status of emergency use of unproven clinical interventions outside clinical trials: Unproven interventions should be used in the context of RCTs or other relevant research activities 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 in monitored emergency use under the MEURI ethical framework. Use under the framework entails adherence to the four categories of justification, ethical and regulatory oversight, consent process and contribution to evidence (see section 2). Interventions offered for emergency use outside clinical trials should not divert attention or resources from effective clinical care, public health measures and clinical trials or other research in the country. Interventions should be offered under emergency use outside clinical trials for a limited time and be transitioned to research, or proven healthcare, as soon as it is possible.

Strengthened ethical and regulatory oversight: Health authorities (national regulatory or other relevant health authority) and ethics committees should become empowered and familiar with the MEURI ethical framework for use of unproven clinical interventions outside clinical trials and ensure coordination for adequate, timely oversight in a public health emergency.

Community engagement: The relevant health authority should proactively communicate to the general population the importance of using interventions that are supported by scientific evidence and of evaluating interventions in research with adequate safeguards (e.g. WHO Solidarity Trial) and also on the risks of unproven interventions. When such interventions are used exceptionally in monitored emergency use protocols,

communications should specify that they have not been fully proven and what that means for different unproven interventions, and seek to promote an open dialogue about the risks and potential benefits and provide information on oversight.

Distinct registry of clinical interventions offered under monitored emergency use: To ensure understanding of the unproven interventions that are offered as research and those as monitored emergency use during a public health emergency, the latter must also be registered. All clinical trial registries – WHO’s International Clinical Trials Registry Platform (ICTRP), registries that provide data for the Platform and national registries that do not – should distinguish between clinical trials (or other research) and protocols for monitored emergency use of unproven clinical interventions (e.g. MEURI).

3.3 Operational recommendations

Scientific basis and qualified scientific committee: A scientific committee must have recommended the proposed intervention under monitored emergency use on the basis of the latest evidence. The committee may be local or international, such as a board of scientific societies that provides advice during a public health emergency. In the case of a PHEIC, recommendations issued by WHO can also be used for this purpose.

Development of a monitored emergency use protocol: The intervention must be proposed as a protocol that includes the following, at a minimum:

- a) background,
- b) scientific justification based on the recommendation of a scientific committee,
- c) objectives and scope of monitored emergency use outside clinical trials,
- d) population to be offered the intervention,
- e) risks and potential benefits,
- f) scientific data on the intervention’s safety and efficacy,
- g) plan for offering the intervention to patients or other recipients,
- h) informed consent forms and details about the process,
- i) plan for ending monitored emergency use protocol and responsible transition,
- j) plan for sharing data and
- k) measures to protect confidentiality and minimize other risks.

Plan for responsible transition: The protocol must also indicate the planned timing or milestones for ending monitored emergency use protocol and for presenting unproven interventions for evaluation in a research protocol (ideally an RCT) or transferring patients to proven, regular health care.

Ethics review and oversight: Even if monitored emergency use does not necessarily entail research, an REC (or an analogous local body) may be best suited for assessing the well-being and safety of recipients of unproven clinical interventions, including the adequacy of the informed consent process, given its similarity to research activities in terms of how it is presented and justified, with the necessary evaluations. In some jurisdictions, appropriately qualified clinical ethics committees may play this role. Although we use REC as the default option, ethical criteria and recommendations for unproven clinical interventions can be implemented by other qualified ethics committees and review systems.

Health authority involvement: The national regulatory or other relevant authority must be aware of which unproven interventions outside clinical trials or other research contexts are being offered and must evaluate and authorize them before the initiation of a monitored emergency use protocol. It is recommended that health authorities collaborate in development of the monitored emergency protocol to ensure the quality and usefulness of the data to be collected. They should also:

- maintain a publicly accessible record of the unproven interventions offered outside clinical trials;
- determine the time necessary to reassess the scientific justification for offering the intervention;
- establish mechanisms and procedures for presenting data collected in the monitored emergency protocol; and
- establish mechanisms and procedures for supervising the intervention, including requesting modification, suspension, termination or transition to research or regular health care.

Registry of monitored emergency protocols: To ensure transparency of access to authorized unproven interventions outside clinical trials, they must be listed in registries that provide data for the International Clinical Trials Registry Platform and other registries that may be locally required. The title of the protocol should indicate clearly that the intervention is offered as a monitored emergency protocol (e.g. MEURI).

Efficiency and coordination: For adequate ethical and regulatory oversight of monitored emergency use, health authorities and RECs must have mechanisms for rapid, efficient communication and coordination. As for research, it is recommended that health authorities and RECs act simultaneously and avoid duplicating efforts (such as review of the same protocol by many RECs). Health authorities, RECs and health-care professionals responsible for access to unproven interventions outside clinical trials should work in close cooperation from the beginning.

Monitoring the intervention: The REC and the national regulatory or other relevant health authority should monitor access to unproven interventions outside clinical trials. The health-care professional or team responsible for the monitored emergency use protocol must reassess the intervention periodically in the light of new evidence and report to the REC and the national regulatory authority at the times and in the manner previously established.

What does the REC review?

The REC reviews:

- a) that the proposed access to unproven clinical intervention outside clinical trials adheres to the criteria of the MEURI ethical framework listed above; and
- b) the ethical and scientific basis of the protocol, including the following:
 - The available scientific evidence based on its risk-benefit balance justifies the intervention.
 - The intervention is offered to the appropriate population.
 - The informed consent process is adequate and pertinent in the context of the public health emergency. The consent document includes details of the interventions and the data that will be collected and also the risks and potential benefits of the unproven intervention.
 - The confidentiality of the data is guaranteed.
 - The data to be collected are relevant for providing information on the safety and efficacy of the unproven intervention. A procedure has been established for sharing data with health authorities and the national and international scientific community rapidly.
 - The plan for ending monitored emergency protocol and responsible transition to routine care.
 - The roles and responsibilities of different parties are defined, such as the party mainly responsible for the emergency protocol, the product sponsor, nongovernmental organizations, universities, health-care centres or hospitals, and possible conflicts of interest are anticipated.

What does the REC oversee?

The REC ensures that the intervention is still justified in the light of new evidence provided in reports from the health-care professional responsible for the intervention. The REC may require modification of the intervention or the way in which it is offered, its suspension or its termination.

4

Questions and answers

Is it ethically permissible to use unproven interventions outside clinical trials during a public health emergency?

During a public health emergency, authorities and health-care workers have, according to their capabilities, an ethical duty to conduct, facilitate or contribute as much as the situation allows to simple, well-designed ethical research, including RCTs, in order to improve the evidence for a systematic response to current or foreseeable disasters, discard unsafe or ineffective interventions and identify interventions that are safe and effective (17). The ethical duty to conduct research has become a legal human rights obligation for WHO Member States to ensure the right to share in scientific advancement and its benefits for all. In particular, the human rights to health and to science include the obligation of States to promote medical research. These are fundamental rights of every human being and are enshrined in articles 25 and 27 of the Universal Declaration of Human Rights and articles 12 and 15 of the International Covenant on Economic, Social and Cultural Rights, respectively (77, 78). On a strictly exceptional basis, however, it may be ethically permissible to use an unproven intervention outside clinical trials for the clinical benefit of individual people or group or to benefit populations if the emergency use meets rigorous ethical criteria (see Table 2, above).

If a proposed use of an unproven intervention does not meet the ethical criteria of the MEURI ethical framework, it is likely to constitute irresponsible use and should not proceed. (For a complete discussion of the ethical framework, see section 2).

What are the challenges that relevant authorities in Member States should consider when allowing emergency use of unproven interventions outside clinical trials?

As recognized by PAHO (22), a key challenge to ethically using unproven interventions outside of clinical trials during the COVID-19 pandemic is lack of or limited adherence to the MEURI ethics framework, for a number of reasons: first, unfamiliarity with the MEURI ethical framework, which was devised for the outbreak of EVD in 2014; and, secondly, the complex correlation of the MEURI ethical framework with different regulatory frameworks and pre-approval access designations (e.g. “off-label” use, expanded access, compassionate use, emergency use authorization), which are not globally harmonized and may not exist in some jurisdictions.

Failure to adhere to the MEURI ethical framework or its appropriate implementation has raised serious ethical concerns, which can be categorized according to the MEURI ethical categories, such as:

Inadequate justification:

- use of unproven clinical interventions, such as those known to be toxic (e.g. chlorine dioxide, methanol), that is not justified by the available evidence and risk–benefit ratio and are thus expected to be more harmful than beneficial (37, 39, 40); and
- excessive assignment of limited resources to unproven clinical interventions with unknown risk–benefit profiles (22).

Inadequate ethical and regulatory oversight:

- undue interference with clinical trials or other necessary research activities (58);
- negligent or intentional mischaracterization by health-care workers, health authorities, ethics committees and other stakeholders of emergency use outside clinical trials, including “off-label” use, as activities

(e.g. “observational research”, “compassionate use”, “quality improvement”) that evade or do not satisfy the justification, oversight, consent and monitoring established in the MEURI ethical framework (22, 24)¹⁵;

- lack of appropriate coordination of use of unproven interventions within and outside clinical trials, including unfair distribution of and access to scarce unproven clinical interventions (58);
- undisclosed conflicts of interest of Member States’ authorities, prescribers and manufacturers (79);
- misuse of unproven interventions outside clinical trials for commercial gain (80);
- exploitation of desperate individuals willing to try any intervention offered, regardless of the expected risks or benefits (16); and
- other harm to third parties due to use of unregulated or underregulated, unproven interventions, including “off-label” uses (e.g. diffusion of unsafe or ineffective unproven interventions, unnecessary stockpiling, creation of shortages of approved medicines for other diseases) (9).

Inadequate consent process:

- invalid or no individual informed consent process when it is required (22);
- undue promotion of unproven clinical interventions outside clinical trials that interferes with appropriate consent (22); and
- irresponsible overstatement of the benefits and understatement of the risks and uncertainties of unproven clinical interventions by national authorities, health-care workers and the media that interferes with the consent process (81).

Inadequate contribution to the generation of evidence:

- failure to use unproven interventions outside clinical trials in a manner that contributes to the generation of evidence (22).

What considerations should be made in evaluating monitored emergency use of preventive unproven clinical interventions outside clinical trials?

Particular care must be exercised in using preventive interventions, as they are usually given to healthy or at-risk groups. Evidence levels of safety and benefit are therefore more important than for therapeutic interventions. Widespread use of unproven interventions outside clinical trials for preventive interventions should therefore be discouraged, as all harm related to the intervention will be iatrogenic.

Possible exceptions include use of chemoprophylaxis in situations in which the probability of harm is exceptionally high, such as known exposure to an infectious agent. It is preferable, however, that clinical trials be organized in these circumstances to generate reliable information. The Working Group considered that ethical guidelines for mass emergency use of novel vaccines for a disease or condition associated with a public health emergency (e.g. novel vaccines for COVID-19) should be addressed in a separate document or documents, given its distinct impact on public health and well-being. The MEURI ethical framework may prove useful for emergency use of such interventions, but it should be adapted to the relevant ethical and regulatory considerations (41–45).

¹⁵ García-Melendez Z. Emergency use of unproven interventions outside the research setting: Analysis of the MEURI ethical framework and challenges for its implementation in El Salvador during the COVID-19 pandemic (unpublished). Buenos Aires: Facultad Latinoamericana de Ciencias Sociales Argentina.

Does health-care workers’ duty of care imply an ethical obligation to use unproven clinical interventions outside clinical trials during public health emergencies?

No. On the contrary, although they may be able to prescribe “off-label” interventions according to national law, the general principle of responsibility is that the less evidence of safety or efficacy of an intervention, the greater the ethical and legal responsibilities of health-care workers and national health authorities to patients (8). By “duty of care”, we understand the obligation of health-care workers to provide care to individuals who are ill and seek assistance. The duty of care is perhaps the ethical foundation of health care.

To fulfil the “duty of care”, health-care professionals should apply their knowledge and skills for the benefit of patients within the limits of the social institution of health care, on the understanding that all medical acts or interventions can benefit or harm patients. Beneficence and non-maleficence must be balanced in every medical act or intervention. Health-care workers have the obligation to use their judgement in order to provide the best possible care to a patient that is consistent with the patient’s expressed wishes (i.e. respect for patient autonomy) and acceptable standards of practice, such as supportive care. It would be a gross misunderstanding to regard the duty of care as independent of ethical considerations of justice or harm to others. Application of unproven interventions to determine their potential benefit to oneself without regard for the potential benefit or harm to others is clearly unethical and cannot be justified by any reasonable interpretation of the duty of care (4).

The provision of care and prescription of medical interventions are not identical. The duty of care does not entail an obligation to use any or all interventions widely and in an uncontrolled manner. The duty of care requires health-care workers to refrain from using interventions that have an established negative risk–benefit ratio. Health-care workers are not obliged to prescribe interventions, either proven or unproven, at the demand of patients or their families, nor are they free to administer any interventions whatsoever.

Is there an ethical obligation to contribute to the generation of evidence during public health emergencies even if research cannot be conducted immediately?

Health care during public health emergencies should be compatible with the ethical obligation to learn from the use of unproven clinical interventions, including “off-label” uses, in order to benefit future patients and to avoid harming them or third parties with unsafe or inefficacious interventions (17, 26). This is the duty to contribute to the generation of evidence and is also recognized in other WHO ethics guidance and related core ethics documents (Table 3).

Table 3. Duty to contribute to the generation of evidence and access to unproven interventions outside clinical trials, including emergency, non-emergency, off-label and compassionate use

Source	Statement	Type
WHO, PAHO (MEURI, EVD, COVID-19)	Contribution to the generation of evidence (MEURI ethical framework, condition 7): “The emergency use of the [unproven] intervention is monitored and the results are documented and shared in a timely manner with the wider medical and scientific community” (16, 20, 22)	Emergency
CIOMS, WHO	Potential individual benefits and risks of investigational interventions and emergency use outside clinical trials. “Even in ordinary circumstances, many promising experimental agents may not be safe and effective, and experimental interventions must be systematically evaluated in clinical trials. [...] Widespread emergency use with inadequate data collection about patient outcomes must therefore be avoided” (17).	Emergency

Source	Statement	Type
WHO	Off-label use of medicines for COVID-19. "It can be ethically appropriate to offer individual patients experimental interventions on an emergency basis outside clinical trials, provided that [...] 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. [...] Where it is possible and feasible for the [off-label intervention] treatment to be given as part of a clinical trial, this should be done unless the patient declines to participate in the trial. If it is not possible to give the treatment as part of a clinical trial, appropriate records of the use of the medicine must be kept, in compliance with national law, and outcomes for patients should be monitored and recorded." (9)	Emergency
WHO	Contribution to the generation of evidence in "compassionate use". "In the particular context of the current Ebola outbreak in West Africa, [...] If and when unproven interventions that have not yet been evaluated for safety and efficacy in humans but have shown promising results in the laboratory and in animal models are used to treat patients, those involved have a moral obligation to collect and share all the scientifically relevant data generated, including from treatments provided for 'compassionate use.'" (12)	Emergency
WMA	Unproven interventions in clinical practice. "[...] This [unproven] intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available." (82)	Emergency and non-emergency

What is appropriate collection and sharing of meaningful data of unproven interventions outside clinical trials, and who is responsible for this?

In clinical trials, the sponsors are generally responsible for appropriate collection and sharing of data with the scientific and clinical community. In emergency use of unproven interventions outside clinical trials, Member States, through their national regulatory and other scientific authorities, are responsible for determining the appropriate means of collecting and sharing data and who is responsible.

When private sponsors (e.g. pharmaceutical companies) conduct clinical trials and are responsible for access to unproven interventions outside clinical trials, they are usually responsible for appropriate collection and sharing of data. Some unproven interventions, however, because of their different proprietary rights (e.g. convalescent human plasma) or other special situations, do not have private sponsors and need governmental or nongovernmental sponsors (e.g. national blood banking and transfusion authority).

Some national authorities and qualified ethics committees (such as RECs) may monitor data and safety; however, most ethics committees, especially in low- and middle-income countries or contexts, are unlikely to have such capacity without appropriate resources, empowerment and familiarization with the MEURI ethical framework. Member States should assume or determine the responsible party for monitoring the use of unproven interventions outside clinical trials and not defer the responsibility on parties without the suitable scientific, ethical or organizational capacity. Appropriate means of collecting and sharing data also include registering monitored emergency use protocols, including informed consent forms and other relevant material, in national and international registries and sharing them with the scientific and medical community (22).

Is there a limit to the number of persons who may receive unproven clinical interventions outside clinical trials?

No. From an ethical point of view, however, use should be limited as much as possible in respect of both time and the number of recipients, especially in uses that would not establish the safety and efficacy of the unproven intervention, such as monitored emergency use protocols. This is necessary in order to avoid any harm to public

health, such as uncontrolled diffusion of unproven, unsafe or ineffective interventions in the health system or interference with the initiation, conduct or completion of research during public health emergencies (5, 65).

Some Member States, national regulatory authorities or health institutions may decide to limit the number of patients who use unproven interventions outside clinical trials to, e.g., 3, 10 or 100 in order to encourage physicians and other health workers to test unproven interventions in well-designed clinical trials (65). One shortcoming of this type of regulatory approach is that there is no limit that will eliminate only harmful or non-beneficial unproven interventions while allowing the development of beneficial interventions (65). Any limit may prove to be too high or too low in different situations or contexts (e.g. different Member States). Others may argue that a limit system is a better “second-best” solution than a more permissive system with no limit at all.

From an ethical point of view, such restrictions should not be inflexible; however, flexibility in regulations should not be unduly exploited to avoid other ethical duties. More specific regulatory design is outside the scope of this ethical guidance.

May health-care workers waive the informed consent process for use of unproven interventions outside clinical trials during a public health emergency?

No. When health-care workers use unproven interventions, they should inform patients that the intervention may not benefit them and may even harm them (22). It is important to remember that consent, in clinical practice or research, is a process and is not equivalent to its documentation (e.g. signing a written document). Any consent process should enable informed consent of patients by ensuring their understanding and that a decision to enrol in a protocol for emergency use of unproven clinical interventions outside clinical trials is made voluntarily, with adequate understanding of the consequences of participation.

When necessary, health-care workers should adapt the documentation of the consent process to the realities of the public health emergency (e.g. using alternatives to written consent). For patients who are unable to give informed consent, proxy consent should be obtained as appropriate, as in any other medical circumstances (22).

Physicians and other health-care workers may have their own opinions about whether a particular unproven clinical intervention is more likely to be beneficial or harmful. A consent process for use of unproven clinical interventions that does not explicitly recognize the scientific community’s uncertainty about the risk–benefit ratio would not, however, be ethically appropriate.

Individual health-care workers and national health authorities must avoid overstating the evidence for unproven interventions. Overstatement of evidence, whether for self-interest or to provide a putative benefit to patients, is contrary to the appropriate consent process for unproven clinical interventions. Hence, community engagement is necessary to prevent undue promotion of unproven interventions outside clinical trials and undue influence on public opinion and the equipoise of the medical community.

How is the MEURI ethical framework related to the WHO EUL procedure?

WHO’s EUL is a procedure for assessing emergency use of unauthorized interventions (vaccines, therapeutics and in-vitro diagnostics) while further data are collected and evaluated. It is thus complementary to the considerations of the MEURI ethical framework. WHO established the “emergency use assessment and listing” procedure in 2015 in response to the outbreak of EVD in West Africa (83) for systematic evaluation and listing

of unlicensed medical products in order to expedite the availability of those products. The procedure was updated and renamed the EUL procedure in 2020 (64) to aid United Nations procurement agencies and the national regulatory authorities of Member States in determining the acceptability of specific unlicensed medical products.

For an intervention to be included in an EUL, the following criteria must be met (43):

- The disease for which the product is intended is serious or immediately life-threatening and has the potential of causing an outbreak, epidemic or pandemic, and it is reasonable to consider the product for an EUL assessment, e.g. there are no licensed products for the indication or for a critical subpopulation (e.g. children).
- Existing products have not been successful in eradicating the disease or preventing outbreaks (in the case of vaccines and medicines).
- The product is manufactured in compliance with current good manufacturing practice in the case of medicines and vaccines and under a functional quality management system in the case of in-vitro diagnostics.
- The applicant undertakes to complete development of the product (validation and verification in the case of in-vitro diagnostics) and apply for WHO prequalification once the data are collected.

As stated in the EUL procedure document (43),

the EUL is not equivalent or an alternative to WHO prequalification, and should not be thought of as such. The EUL is a special procedure for unlicensed vaccines, medicines and in vitro diagnostics in the event of a PHE [public health emergency of international concern or other public health emergency authorized by the Director-General] when the community/public health authorities may be willing to tolerate less certainty about the efficacy and safety of products, given the morbidity and/or mortality of the disease and the lack or paucity of treatment, diagnosis/detection or prevention options. It is intended to provide a time-limited listing [...] for unlicensed products in an emergency context when limited data are available and the products are not yet ready for application for prequalification. As part of the EUL, it is expected that the manufacturer will complete the development of the product and submit for licensure and WHO prequalification.

The document also states that

WHO has developed the EUL process to expedite the availability of unlicensed medical products needed in public health emergency situations, to assist interested UN procurement agencies and Member States in determining the acceptability of using specific products in the context of a public health emergency, based on an essential set of available quality, safety, and efficacy/immunogenicity/ performance data. The EUL is not intended to interfere with ongoing clinical trials. This means that the clinical development should proceed as planned after the initial submission and subsequent updates. WHO-Member States have the sole prerogative to use the EUL as the basis to authorize the use of an unlicensed vaccine/ medicine/in-vitro diagnostics at the national level [original emphasis].

How should Member States view research?

Member States should consider their spending on human health research capacity as an essential investment in the well-being of the population, public health and development and not a mere expense. This is consistent with the idea that research is a societal public good, and additional knowledge is a public good that can be supported through an appeal to solidarity (72). Research during public health emergencies is at the same time an ethical duty and a human rights obligation of all Member States (see question 1).

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Annex 1. Brief chronology of the development of the MEURI ethical framework for emergency use of unproven clinical interventions outside clinical trials (2014–2020)

This annex provides a brief, non-exhaustive chronological reconstruction of the development of WHO's ethical framework for emergency use of unproven clinical interventions outside clinical trials.¹ More research should be conducted on the historical and ethical background of the WHO MEURI ethical framework.

1. The West African Ebola virus disease (EVD) outbreak (2014): Background to the WHO's ethical framework for emergency use outside clinical trials

The 2014–2016 outbreak in West Africa was the largest, most complex outbreak of EVD since the virus was first identified in 1976, with more cases and deaths than in all the other epidemics combined. It also spread among countries, starting in Guinea (December 2013) then moving across land borders to Sierra Leone and Liberia. On 8 August 2014, WHO issued an online press release (2) explaining the background to the first panel discussion on ethical considerations for use of unregistered interventions for EVD, in which some health workers infected with the virus received unproven clinical interventions outside clinical trials:

The recent treatment of two health workers infected with the Ebola virus with experimental medicine has raised questions about whether medicine that has never been tested and shown to be safe in people should be used in the outbreak, and, given the extremely limited amount of medicine available, if it is used, who should receive it. A number of interventions have been through the laboratory and animal study phases of development. It is likely that 'first in man' studies will be conducted over the next 2–4 months. It is also likely that the number of doses available for further study and/or deployment from end 2014 onwards will remain insufficient to meet demand. On Monday, August 11, WHO is convening a panel discussion of medical ethicists, scientific experts and lay people from affected countries to assess the role of experimental therapies in the Ebola outbreak response. Issues to be considered include:

[1] Whether it is ethical to use unregistered interventions with unknown adverse effects for possible treatment or prophylaxis. If it is, what criteria and conditions need to be satisfied before they can be used?

[2] If it is ethical to use these unregistered interventions in the circumstances mentioned above, then what criteria should guide the choice of the intervention and who should receive priority for treatment or prevention?

This official background is complemented by a more detailed account from one of the members of the first Working Group (3):

International attention and concern about the EV [Ebola virus] outbreak intensified in early August 2014. Two American medical missionaries received an experimental monoclonal antibody. The means by which

¹ Substantive parts of this annex are from reference (1).

the nongovernmental organization Samaritan's Purse was able to access the experimental agent remains obscure. Shortly after, a Spanish missionary and two Liberian physicians also received the agent. In each case the language of compassionate use was invoked as justification. As a result, no ethical criteria, protocol, or reasons of any kind were used to determine who would get the very small supply of the untested agent. Ethics seemed to have vanished. Furthermore, there has been no mention of a standardized data set to evaluate the impact of the untested agent. Hence the goals of science were similarly undermined. The lack of transparency for access and the rapid deployment of "novel therapies" triggered an immediate outcry in the media. The World Health Organization promptly announced that it would convene a panel of ethicists to address the issues associated with the use of investigational agents. The panel was tasked with answering five questions, but the questions essentially boiled down to whether it was permissible to use unregistered interventions with no human data to support safety or efficacy.

2. The West African EVD outbreak (2014): "compassionate use" and the pre-MEURI ethical framework

On 11 August 2014, in the context of the West Africa EVD outbreak, WHO convened a panel of experts (4) to answer a number of questions, which were summarized by a second working group. One question was, "Is it ethically permissible to use scientifically promising but unproven interventions (outside clinical trials) for treatment and prevention? If so, what are the conditions and criteria for their use?" (5). The first expert panel reached consensus that it was ethical to offer unproven interventions outside clinical trials if the interventions adhered to a set of eight ethical criteria (2, 6):

- transparency about all aspects of care,
- informed consent,
- freedom of choice,
- confidentiality,
- respect for the person,
- preservation of dignity and
- involvement of the community.

To monitor the safety and efficacy of the emergency use of unproven clinical interventions outside clinical trials, the panel advised (2) that:

- if and when they are used to treat patients, there is a moral obligation to collect and share all data generated, including from treatments provided for "compassionate use" (access to an unapproved drug outside of a clinical trial).

Of the list of eight criteria, the last one (associated with "data collection and sharing", "duty of contribution to the generation of evidence" and "monitoring") gave the salient characteristics to the yet to be coined term "monitored emergency use of unregistered and experimental interventions" (MEURI).

3. The West African EVD outbreak (2014–2016): origin and development of the MEURI ethical framework

On 20–21 October 2014, during the EVD outbreak in West Africa, a second WHO advisory panel coined the term MEURI (5) to refer to a new mechanism created as a bridge to clinical trials in order to curb unjustified, excessive

use of unproven interventions and to avoid the misleading “compassionate use” designation (6). The second working group was convened in response to criticism of the first working group (3):

The [first] panel was criticized for the haste in which it was brought together and the lack of representativeness. These shortcomings have been acknowledged; however, there has been little disagreement with the substantive decision. The subsequent, larger panel has good representation of ethicists and social scientists from West Africa.

On 5 November 2014, detailed interim guidance for potential EVD therapies and vaccines was published (8), with seven annexes. The guidance included a detailed list of examples of unproven interventions, a section on research and accelerated authorization and a section on communication during the outbreak. A section on “Evaluation and emergency/compassionate use of unproven interventions” (7) included the following:

3. Evaluation and emergency/compassionate use of unproven interventions
 - 3.1. Objectives of the plan for emergency use and assessment (if appropriate) of unproven interventions
 - 3.2. Proposed criteria for assessing the likely value of the compassionate use/assessment of lead experimental therapies and vaccines
 - 3.3. Major regulatory considerations for emergency/compassionate use
 - 3.4. Major ethical issues for consideration in the context of emergency/compassionate use
 - 3.5. Major issues regarding data collection outside of RTCs
 - 3.6. Major issues in relation to risk assessment and risk mitigation and management
 - 3.7. Major logistics considerations for each investigational therapy and/or vaccine
 - 3.8. Preliminary considerations regarding management of future supplies.

The interim guidance referred to the work of the first working group but not to that of the second and therefore did not include the term MEURI, but did include the term “emergency use”.

The WHO Guidance for managing ethical issues in infectious disease outbreaks, also known as the “green book” for the colour of its cover, is one of the most authoritative guidance for the ethics of pandemic preparedness and response (8, 9). Guideline 9, “Emergency use of unproven interventions outside of research” (and cross-references from guideline 4 “Allocating scarce resources”, 10 “Rapid data sharing” and 13 “Frontline response workers’ rights and obligations”) is considered the core of the first version of the MEURI ethical framework. The framework shows that it is ethically permissible to use unproven interventions in an emergency outside clinical trials, provided that seven ethical criteria are met:

- no proven effective treatment exists;
- it is not possible to initiate clinical studies immediately;
- 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 favourable risk–benefit analysis;
- the relevant country authorities, as well as an appropriately qualified ethics committee, have approved such use;
- adequate resources are available to ensure that risks can be minimized;
- the patient’s informed consent is obtained; 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 (10).

The MEURI framework also states that emergency use of unproven interventions outside clinical trials should be guided by a set of seven ethical principles, namely, independent oversight, effective resource allocation,

minimizing risk, collection and sharing of meaningful data, informed consent, need for community engagement and fair distribution in the face of scarcity (10). It also included an ethical justification for MEURI:

Ethical basis for MEURI – MEURI is justified by the ethical principle of respect for patient autonomy – i.e., the right of individuals to make their own risk–benefit assessments in light of their personal values, goals and health conditions. It is also supported by the principle of beneficence – providing patients with available and reasonable opportunities to improve their condition, including measures that can plausibly mitigate extreme suffering and enhance survival.

It should be noted that the justification may be regarded as incomplete, as it does not present ethical considerations (e.g. justice, non-maleficence, harm to third parties, other public health ethics considerations) to justify the seven conditions and seven principles of the framework, which limits considerations of individual autonomy and beneficence.

4. Outbreak of EVD in the Democratic Republic of the Congo (2017–2020): coexistence of MEURI and ethical frameworks for expanded access

In a meeting on 25–27 April 2017, the WHO Strategic Advisory Group of Experts on immunization (SAGE) evaluated the state of development of candidate vaccines for EVD and recommended (11) that:

Should an Ebola disease outbreak occur before the candidate vaccine is licensed, SAGE recommended that the rVSVΔG-ZEBOV-GP vaccine be promptly deployed under the expanded access framework, with informed consent and in compliance with good clinical practice. If the outbreak is caused by an Ebola virus species other than Zaire, consideration should be given to the use of other candidate vaccines that target the putative viral species.

The Group did not refer specifically to the MEURI framework. The inclusion in this chronology, however, is justified in that there is no practically relevant difference, as both the expanded access and the MEURI ethical frameworks are part of the ethics of emergency use outside clinical trials in WHO documents.

On 11 May 2017:

the Ministry of Health of the Democratic Republic of the Congo (DRC) informed the World Health Organization (WHO) of a laboratory confirmed case of EVD. The outbreak occurred in the Likati Health Zone – a remote area with limited access to transport and communication infrastructure. The outbreak was declared over on 2 July 2017 with a total of five confirmed and three probable cases, with four deaths and four survivors. The outbreak was controlled through existing well-defined EVD response interventions [...]. In addition, as done previously during the Ebola outbreak in Guinea and Sierra Leone, a candidate EVD vaccine (rVSVΔG-ZEBOV-GP) was available under an expanded access framework as recommended by SAGE. The Government of the DRC, together with MSF and WHO, were ready to deploy the vaccine should its use be indicated. Although the vaccine was ultimately not deployed, important lessons were learned in the preparations undertaken by all partners (11).

On 18–19 September 2017, a workshop on expanded access to experimental EBV vaccines was held to define, explain and justify the expanded access/compassionate use framework for vaccines, differences between mass

and ring vaccination strategies,² good clinical practice, communication strategies and other topics (11). There was no explicit mention of the MEURI framework, but one of the participants mentioned ethical conditions for emergency use outside clinical trials similar to those of the first WHO Working Group in 2014.³

On 17 May and 27 August 2018, a group of independent scientific experts was convened by WHO to evaluate the ethical permissibility of emergency use of unproven interventions outside clinical trials for EVD (13, 14). Both documents restrict the scope of the ethical analysis to unproven therapeutic interventions and do not include vaccines. The group mentioned the MEURI ethical framework and the seven ethical criteria for permissible monitored emergency use in the green book (11). The expert panel stated that, while it is appropriate to provide “investigational agents” under MEURI, efforts should be made to minimize possible interference in the initiation, conduct or completion of RCTs for evaluation of investigational therapeutics for treatment of patients with EVD (14). They stressed that RCTs would be the best means of evaluating investigational therapies and identify the therapies that could benefit patients with EVD (14). They also presented a scientific assessment of a number of unproven therapeutical interventions – ZMapp, remdesivir (GS-5734), REGN-EB3 (REGN3470-3471-3479), Mab114 and Favipiravir – which include monoclonal antibodies and antiviral drugs, and determined which could be considered for use within the MEURI ethical framework (14). The panel also affirmed the importance of conducting appropriate clinical trials as soon as possible (14).

According to the WHO Regional Office for Africa (15), since the start of the EVD outbreak in the Democratic Republic of the Congo in August 2018:

patients have had access to one of four investigational treatments on a compassionate basis. These drugs – mAb 114, remdesivir, Zmapp and REGN-EB3 – were offered under an ethical framework developed by the World Health Organization known as the Monitored Emergency Use of Unregistered Interventions protocol. By 1 January, 248 patients had received one of these four drugs. While some patients seemed to improve, there was no scientific evaluation of the efficacy and safety of these drugs.

The lack of “scientific evaluation” of the safety of the unproven interventions mentioned above resonates with subsequent identification by PAHO of the challenge of limited adherence to the MEURI ethics framework, in this case, the ethical criterion of monitoring for safety or more broadly the ethical obligation of contributing to generation of evidence.

In November 2018, the emergency use protocol was terminated and these four unproven clinical interventions used under the MEURI ethical framework were transitioned to an RCT. According to the Regional Office for Africa (15):

[...] on 24 November, the DRC Ministry of Public Health announced the start of a randomized control trial. WHO is coordinating the trial which is led and funded by the Institut National de Recherche Biomédicale and the National Institutes of Health, a part of the US Department of Health and Human Services. Other partners are Médecins Sans Frontières and ALIMA [health nongovernmental organizations].

² The ring vaccination strategy with experimental vaccine during the EBV outbreak in the Democratic Republic of the Congo should be distinguished from mass vaccination with an experimental vaccine for COVID-19 during the current pandemic. For a distinction between ring vaccination during an outbreak and usual mass vaccination, see 13.

³ “Ethical considerations for using vaccines under an Expanded Access Framework and how to involve ethics committees. The protocol for using an unlicensed vaccine in the context of a public health emergency must be clearly identified as either a ‘treatment’ protocol or a research cohort protocol. Even though collecting safety and efficacy data is an ethical requirement, it is not the primary purpose of the protocol under an Expanded Access Framework. This has important implications for the consent process required, as participants must be asked to consent to accepting the vaccine as well as to providing data for safety and efficacy studies. Ethical criteria that must be considered include transparency, fairness, informed consent, freedom of choice, confidentiality, respect for the person, preservation of dignity, involvement of the community and risk-benefit assessment. The protocol must be accompanied by clear messaging and community engagement. Plans to ensure fair and equitable sharing of vaccine doses should be developed, and hard-to-access and vulnerable populations (including pregnant women and children) included where possible to ensure fairness. Ethics committees should be involved early on in order to fully understand and advise on the issues involved.”

This transition provided valuable scientific results (e.g. 16). In the response to the EVD outbreak in the Democratic Republic of the Congo, the language of MEURI (for unproven therapeutic and preventive interventions) and expanded access/compassionate use (for unproven preventive interventions, in particular vaccines) was used to organize emergency use outside clinical trials.

5. The COVID-19 outbreak (2020-to date): The MEURI ethical framework

In the context of the COVID-19 pandemic, WHO published at least two important documents related to the MEURI ethical framework. On 31 March 2020, a press release, “Off-label use of medicines for COVID-19” was published describing use of the MEURI ethical framework, although it sometimes refers to “compassionate use” (17). This short press release presented a slightly modified set of ethical criteria from WHO’s green book (10) and recommendations for implementation. Its publication coincided with a surge in “off-label” use of proven interventions for COVID-19, such as the US Food and Drug Administration emergency use authorization for chloroquine and hydroxychloroquine on 28 March, which, however, was revoked for lack of evidence on 15 June (18). On 25 June, PAHO (19) issued a document “Emergency use of unproven interventions outside of research: Ethics guidance for the COVID-19 pandemic”, in which it further advanced the MEURI ethical framework, with classification of the seven ethical criteria into four categories, justification (criteria 1–3), ethical and regulatory oversight (criteria 4 and 5), consent process (criterion 6) and contribution to generation of evidence (criterion 7). PAHO included therapeutic and preventive uses of both completely unproven interventions (e.g. remdesivir) and “off-label” interventions (e.g. hydroxychloroquine). Moreover, it provided additional guidance for use of the MEURI ethical framework, identification of challenges that might arise due to lack of adherence to the MEURI framework, comments on the categories of the framework and general and operational recommendations for its implementation. Below is an abridged table of PAHO’s revision of the seven MEURI ethical criteria (from 11).

Justification
<ul style="list-style-type: none"> • no proven effective treatment exists; • it is not possible to initiate clinical studies immediately; • 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 favourable risk–benefit analysis;
Ethical and regulatory oversight
<ul style="list-style-type: none"> • the relevant country authorities, as well as an appropriately qualified ethics committee, have approved such use; • adequate resources are available to ensure that risks can be minimized;
Consent process
<ul style="list-style-type: none"> • the patient’s informed consent is obtained; and
Contribution to the generation of evidence
<ul style="list-style-type: none"> • 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.

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Annex 2. Brief explanation of the MEURI ethical framework for use in newsletters or other communications

During public health emergencies, it can be ethically appropriate exceptionally to offer unproven interventions outside clinical trials, including “off label” uses, provided that four ethical categories are met: justification, ethical and regulatory oversight, consent process and contribution to the generation of evidence. The MEURI ethical framework provides a detailed analysis of each of these four ethical categories as well as recommendations for its implementation.



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