Guidance for ethics oversight of COVID-19 research in response to emerging evidence

I. Introduction

Health-related research with human subjects is an essential component of the response to the COVID-19 pandemic. All research should be reviewed and approved by a research ethics committee (REC) before its initiation in order to guarantee its social and scientific value as well as its ethical conduct, including respect for participants' rights, security, and wellbeing. RECs have the responsibility to carry out ethics reviews rapidly and approve research protocols that adhere to ethical standards after a rigorous analysis (*1-3*). The ethical acceptability of research can vary throughout its duration. For example, a study can cease to have social value if the question it aims at answering has been answered by another study with high quality evidence. A study can cease to have a favorable risk/benefit ratio if the study intervention is found to be riskier than initially thought, or if an effective treatment has already been found for the condition studied. A consent process could also cease to be adequate if it does not inform potential participants about alternative treatments that are now available and were not available before. Therefore, once a study begins, RECs should oversee its development up until its conclusion (*1-3*).

The pandemic poses additional challenges. Investigators should continuously evaluate, in a timely manner and on the basis of up-to-date available evidence, the justification for their studies and the conduct of such studies in the way in which they were approved. This duty is part of the ethics oversight of studies that RECs carry out. This document aims to guide the ethics analysis and procedures for the oversight of COVID-19-related research in light of the rapid production of evidence during the pandemic.

II. Challenges of ethics oversight during the pandemic

In the context of the pandemic, the oversight of ongoing COVID-19 research should be carried out more often than usual due to the great speed at which new scientific evidence is being produced. This rapid production of evidence, which is crucial to improving the response to the pandemic, can impact the social and scientific value of COVID-19 studies, their risk/benefit balance and other aspects of their ethical acceptability. This has occurred, for example, with studies that test hydroxychloroquine as a possible treatment for COVID-19. After the results of the RECOVERY trial showed its futility to treat COVID-19 in hospitalized patients (4), other ongoing studies testing this drug had to be revised for changes or suspended; among these, the *Solidarity* clinical trial of the World Health Organization (WHO) ended up closing the arm that studied hydroxychloroquine (5). Consequently, clinical trials studying the efficacy of this drug

that were ethically acceptable at their initiation can cease to be so in light of this new evidence. Given the great number of studies that are being carried out about COVID-19, such changes can occur on much shorter timelines than usual.

Investigators are responsible for continuously updating their knowledge related to the study and, especially, for reviewing the available scientific evidence at appropriate intervals. Importantly, decisions must be always made on the basis of high quality scientific evidence, which in turn depends on rigorous study designs, consistency of the results, precision resulting from confidence intervals, lack of bias, etc. (*6*). To update their knowledge, investigators can draw from the latest systematic reviews and meta-analyses of scientific evidence by entities such as Cochrane, recognized institutions that synthesize evidence such as those that are part of the Covid-19 Evidence Network (COVID-END) (*7*), or international organizations such as the Pan American Health Organization (PAHO) and WHO (*8*), as well as quality available scientific literature. Investigators should distinguish the quality of the evidence they evaluate and keep in mind that the value of available evidence can vary in a short time period. It must be taken into account that there may be knowledge gaps in the evidence for subgroups or specific populations. Investigators are therefore advised to be attentive to the different types of publications related to one's study that are emerging (including *pre-prints*) and preferably make decisions on the basis of studies published in peer-reviewed scientific journals.

RECs must review the protocol in question in light of newly available scientific evidence, as well as evaluate and approve the measures investigators have adopted to guarantee that a study will continue adhering to ethical standards.

With the emergence of new scientific evidence that could affect the justification for the research or its conduct as established in the protocol:

- Investigators should evaluate whether to continue, modify, suspend or cancel the study, and swiftly inform the REC about their proposed course of action.
- RECs should review the protocol, as well as evaluate and approve, if appropriate, the measures proposed by investigators to guarantee that the investigation continues adhering to ethical standards.

III. Operational recommendations for ethics oversight

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

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

The report on evidence that investigators present to the REC should include a summary of the most important points of their review and the references consulted. Amid this new evidence, investigators should justify whether they should: a) continue the study b) carry out modifications to the study, c) suspend the study or, d) cancel the study.

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

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

To assess the continuation or modification of a study, the REC should review the report that was presented and analyze whether it is pertinent to approve the study's continuation, approve the proposed modifications, request additional modifications, temporarily suspend or cancel the study. Once the REC approves the modifications, the investigators should quickly take any necessary actions, for example, obtaining new consent from the participants if it had been stipulated by the REC to do so.

If the REC decides to modify, suspend or cancel the study, investigators must communicate this decision immediately to the relevant health authorities. They should also record these changes as soon as possible in the respective research registries, including those that are part of WHO's International Clinical Trials Registry Platform (ICTRP). In the case of the suspension or cancellation of the study, investigators should communicate this decision to the scientific community and the general public. The REC should also make public the suspension or cancellation of the study (for example, publishing the information in its web page) and informing the other involved institutions, RECs or networks of RECs they belong to about this decision

Just as in non-pandemic times, investigators should employ community engagement strategies to communicate the new information about the study in a transparent way. In addition, amid the proliferation of information about new evidence in mass media and social networks, the urgency to keep participants continually informed is greater than ever. It is also urgent to inform the general population since this is key to mitigating their concerns and clearing up misunderstandings that could lower their trust in research.

IV. Guiding questions for ethics oversight

To justify continuing, modifying, suspending or cancelling a study, an ethics analysis should be carried out in light of new evidence. Below are some questions that can guide the ethical analysis that is part of the oversight of research, which have been developed on the basis of an existing ethics review framework (*9-11*).

Social value	● Taking into account the newly available evidence, does it continue being valuable to carry out this study in this particular context? ● What is the expected benefit of this study that is different from the benefits achieved by other similar studies that have been completed? ● Has the research question already been answered (totally or partially)? If so, does this answer take into account the relevant endpoints? ● Should a change in the objectives of the study be considered?

Scientific value	● Taking into account the newly available evidence, is the methodological design still adequate to respond to the research question? ● Is the control mechanism in the study still appropriate in light of newly available evidence? ● Taking into account the newly available evidence and the current context (for example, the epidemiologic context), is it still feasible to carry out the study?

Fair participant selection	● On the basis of newly available evidence, should inclusion and exclusion criteria be modified to minimize risks for participants and maximize the potential benefits of the study?
	● To evaluate if it is appropriate to modify the inclusion and exclusion criteria, it should be considered whether previous studies have demonstrated, for example, that the study intervention:
	  ○ Is risky for a subgroup.
	  ○ Is beneficial only for a subgroup.
	  ○ Is harmful for a subgroup.

Favorable risk/benefit ratio	● Taking into account the new evidence: does it the risk-benefit balance continue being favorable? Are there new risks? Are these risks justified in light of the study's potential benefits? Does the study have the potential for greater or different benefits from those that were initially considered?
	● To evaluate if the risk-benefit balance continues being favorable, it should be considered whether previous studies had demonstrated, for example, that the study intervention:
	  ○ Is riskier than previously considered to be.
	  ○ Is harmful.
	  ○ Has no benefit.
	  ○ Has limited benefits.
	  ○ Has additional benefits than those previously considered.
	● Based on currently available evidence, should other measures be adopted to minimize risks or maximize the benefits of the study?

Informed consent	● Is there new information that could affect participants' decision to continue in the study; for example, regarding risks of the intervention under study? How will this information be provided to participants? ● Has a modification of the protocol been identified, about which potential participants or those that were already enrolled in the study should be informed? ● Is it necessary to obtain a new consent from participants?

Respect for participants	• Is there new evidence that participants should be informed about? Does this evidence impact the conduct of the study in such a way that it should be required for participants to be informed about it? • In light of newly available evidence, should additional or different measures be considered to monitor the wellbeing of participants throughout the study? • After having decided to that the study should be suspended or cancelled, how should participants be informed?, how will their safety and well-being be guaranteed, what medical care will they receive and how will it be ensured that they are covered for eventual harms that may result from the study? • If an effective intervention is discovered in other studies, will this intervention be given to participants in the study in question?

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