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COMMENTARY

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A Call for Better, Not Faster, Research Ethics Committee Reviews in the Covid-19 Era

Public health emergencies commonly raise ethical dilemmas, but few emerging infectious diseases have posed so many ethical challenges as rapidly as has SARS-CoV2, the virus that causes Covid-19. The ethical challenges range from access to the health system to allocation of diagnostic, preventive, and treatment strategies.[1] While some of these challenges have been much discussed in the ethics literature, little has been said about the role of research ethics committees (RECs)—known as "institutional review boards" (or "IRBs") in the United States—in public health emergencies and the special issues they have been facing during the Covid-19 pandemic.

Because of the rapid spread of SARS-CoV2 and the unprecedented impact on daily lives and medical resources, government agencies, the scientific community, and private and public sponsors have facilitated research on Covid-19, leading to a rapid proliferation of research studies. With all these studies requiring review by RECs, this dramatic increase within a very short time has placed a significant strain on RECs. In addition to the increased volume, these committees face pressure to move through the review process quickly so that studies can get underway to address the pandemic. RECs in China have reported meeting four times a month and have a mean time of two days from submission to approval,[2] while other countries have reported that Covid-19 ad-hoc committees have slowed approval and research.[3] There are also calls for RECs to increase efficiency without relaxing the standards for ethical review.[4] RECs are accustomed to external pressure for approval from investigators, most often because investigators need approval to get funding from the sponsors of their studies. However, in the Covid-19 era, this pressure is increasing and coming from not only the sponsors and investigators but also many other stakeholders, including world leaders, the community, the media, and professional organizations.

Besides the external pressure and excessive number of studies, there are inherent challenges when reviewing Covid-19 research studies. The challenges can directly affect the application of the Belmont principles of respect for persons, beneficence, and justice. Here, we describe some of those challenges that we have experienced in our work on a central REC reviewing complex multicenter Covid-19 studies and also discuss some of the issues that RECs have to address in their deliberations.

ENSURING APPROPRIATE SCIENTIFIC REVIEW

Reviewing a protocol's research methods and scientific validity is not a task for IRBs described in the federal regulations governing research with humans (the "Common Rule"). However, assessing the scientific merit of a research protocol is the primary means of establishing the beneficence and nonmaleficence of a study. Scientific review has often been an unofficial task of the REC, especially when an official scientific review by another body, such as a grant review committee, is unavailable or cursory. With the efforts to rapidly identify and test new potential treatments for SARS-CoV2, substantive, albeit not protracted, scientific vetting is even more essential. Poorly designed research can unnecessarily increase risk exposure to participants, and inconclusive studies can further delay advances against Covid-19 and waste valuable resources.

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The main challenge for RECs in the face of a new infectious disease is making sure that RECs have members or consultants with expertise in infectious diseases and public health preparedness so as to ensure that a proposed study is based on enough preliminary data to justify the research and will have an appropriate sample size and randomization scheme. Yet when an REC does not have sufficient expertise, we have found that a quality scientific review conducted by a scientific review committee in close association with the REC review allows the REC to more properly evaluate the safety, ethics, and processes while eliminating delay due to uncertainty about the science.

DOCUMENTING INFORMED CONSENT

The main challenge for obtaining informed consent from individuals who agree to enroll in studies on potential Covid-19 treatments lies in the contagious nature of SARS-CoV2. Documenting informed consent in the traditional sense from a patient with Covid-19—by using a paper consent form and requiring the patient's signature on the form—can be difficult and could involve the risk of infection of the person conducting the consent process. And if a medical center has limited access to visitors, even obtaining signed consent from a patient's legally authorized representative when the patient cannot give consent due to being incapacitated will be a challenge. Even though in the United States using electronic methods to obtain consent is permissible when certain conditions are met, it is not always possible to use such methods. When electronic methods of documenting consent are unavailable, the U.S. Food and Drug Administration (FDA) has proposed that the research team conduct the informed consent process with an impartial witness. The FDA recommends an attestation by a witness or the use of smartphones to record the signature on the informed consent document. Since there is currently little flexibility in FDA guidance, adhering to it can certainly become a cumbersome process, as either of these steps adds an extra layer of documentation.

However, if the research team obtains a waiver from the IRB for the documentation of informed consent, we believe that informed consent can be achieved by providing an information document to the participant and allowing a third-party witness to confirm the patient's agreement. This process can ensure that the ethical principle of patient autonomy can be maintained while minimizing the physical exposure and risk between researchers and participants.

MINIMIZING RISK

For clinical trials of potential Covid-19 treatments, the main challenge in minimizing risk is the lack of preliminary data about the new investigational agents. Many investigational agents under consideration for trials are FDA-approved drugs being "repurposed" for testing against Covid-19. Thus, they have limited safety data in the Covid-19 population and little, if any, evidence of efficacy. RECs must ensure that research protocols are scientifically and medically valid and that, if FDA approval is required for a clinical trial, the study team has obtained it. RECs must also ensure that studies have a data safety monitoring board (DSMB) and/or are subject to frequent, regular review of study-related adverse events so that the studies can be quickly halted or changed if necessary.

In the Covid-19 era, RECs must also consider risk to the research team. Researchers are potentially susceptible to infection due to Covid-19 contagion. We have sought to make the safety of researchers an REC consideration by ensuring that any researchers who come in contact with Covid-19-positive participants are monitored in the same way as clinical staff who have contact with Covid-19-positive patients are. If a study team member tests positive for Covid-19, this should be reported as an unanticipated problem to both the REC and the DSMB.

PROTECTING THE VULNERABLE

Although patients with Covid-19 do not meet the Common Rule definition of a vulnerable population, many of them can be perceived as vulnerable since the disease disproportionally affects people from racial and ethnic minority groups, the economically disadvantaged, the elderly, and those with certain medical conditions.[5] The isolation of Covid-19 patients from their families and the lack of treatments for the disease could make patients vulnerable to being unduly induced to participate in clinical trials. RECs should discuss this issue in their review of protocols and consider whether

special protections during the recruitment process and throughout a trial are needed for these populations.[6]

RECOMMENDATIONS

This commentary has highlighted the challenges for RECs when reviewing protocols for Covid-19 studies. The recommended steps that RECs can take when reviewing Covid-19 protocols will apply to research that emerges during future infectious disease outbreaks. The following are reasonable simple initial steps:

- Ensure appropriate scientific review of protocols. If there has been a scientific review by another committee, request notes from the review so that REC members can see if specific issues of concern have been addressed. If there has not, request a rapid scientific review and, if possible, allow one or more members from the REC to observe the review and/or ask prior to the review that specific issues be addressed.

- Dedicate an existing REC to Covid-19-related review. Use alternate members and consultants as much as needed. Alternatively, a current REC could meet more often or on an ad hoc basis, devoting these extra meetings to review of Covid-19 studies. Importantly, continue to review these studies with the same rigor and principles as if this were not a pandemic.

- Facilitate the conduct of sound scientific and ethical research. The REC can be the conduit for open communication among the REC, researchers, scientific review group, institution, and sponsor to address concerns and to problem solve to streamline protocol revisions.

- Reconsider the evaluation metrics of the REC. Time to approval should not be the primary metric in the Covid-19 era. Satisfaction of all stakeholders should be considered: this includes participant satisfaction with the informed decision process and their contribution to the research, investigator satisfaction with the efficiency of the process, and committee satisfaction that a thorough and ethical review was conducted.

RECs face a very difficult task in making sure the ethical principles of *The Belmont Report* are upheld, even in the face of tremendous internal, external, and even personal pressures to address the unprecedented impact of Covid-19. High-quality ethical research is the key to ending this pandemic. It is important to ensure ethical research and not to abandon the long-held principles of ethical review and protections for research participants.

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DISCLOSURES

The authors are the cochairs of the Veterans Affairs (VA) Central Institutional Review Board (IRB) panels and the VA Central IRB administrator. The views expressed in this perspective paper are not those of the VA Central IRB, the Department of Veterans Affairs, or the federal government.

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