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SPECIAL ARTICLE

Challenges in Research Practices during COVID – 19 Pandemic

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ABSTRACT

The current emergence of the Covid-19 pandemic brought global disruption to every aspect of society including health, supply chain, the economy, social interaction and research practice. Conducting research in epidemic situations is challenging to researchers because they must respond to the needs and trust of the public so a knowledge base must be built quickly. The appropriate role of research during the outbreak involves allocating limited healthcare resources appropriately, and remains based on the relevant ethical principles of respect for person, beneficence, justice, utility, liberty, reciprocity and solidarity. All researchers, research institutions, research ethics committees, national regulators, international organizations and commercial sponsors, have an obligation to ensure that the challenge studies are carefully designed and ethically conducted in outbreak situations.

Keywords: Covid-19, Pandemic, Research ethics, Challenge study, Ethics committees.

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Introduction

During the Covid-19 pandemic a moral obligation requires authorities to learn as much as possible as quickly as possible, to inform the ongoing public health response, and to allow for proper scientific evaluation of new interventions being tested. Several ethical issues have arisen in clinical research during the COVID-19 pandemic(1). The appropriate role of research during the outbreak involves allocating limited healthcare resources appropriately, and remains based on the relevant ethical principles of respect for person, beneficence, justice, utility, liberty, reciprocity and solidarity. With regards to fair allocation of scarce resources during the COVID-19 outbreak, recommendations have been made in line with the utilitarian approach of maximizing benefits and are based on four guiding principles: (1) maximizing total benefits produced by scarce resources, (2) treating equivalent cases equally, (3) promoting and rewarding instrumental value (benefit to others) and (4) giving priority to the worst off(2).

Research conducted during the COVID-19 outbreak should be designed and implemented in conjunction with other public health interventions.

Under no circumstances should research compromise the public health response to an outbreak or the provision of appropriate clinical care. All clinical trials must be prospectively registered in an appropriate clinical trial registry(3). As in non-outbreak situations, ensuring that studies are scientifically valid and add social value is essential; given that risks are reasonable in relation to anticipated benefits; that participants are selected fairly and participate voluntarily (in most situations following an explicit process of informed consent); that participants' rights and well-being are sufficiently protected and that studies undergo an adequate process of independent review(4). These internationally accepted norms and standards stem from the basic ethical principles of respect for person, beneficence, and justice(5). They apply to all fields of research involving human beings, whether biomedical, epidemiology, public health or social science studies, and are explained in detail in numerous international ethics guidelines(4-8) all of which apply with full force in outbreak situations. All researchers, research institutions, research ethics committees, national regulators, international organizations, and commercial sponsors have an obligation to ensure that these principles are upheld in outbreak situations(3).

In the immediate aftermath of the declaration of the pandemic, and government guidance for social distancing as public health measures to prevent or slow the spread of disease, trial sponsors, academic institutions and investigators were required to determine whether ongoing trials should proceed and if so, what modifications would be needed, suspended or discontinued altogether. These determinations were made considering several factors, including trial location, the indication for the trial, the urgency of continuation, the safety of participants and healthcare workers and risks to trial integrity. Any consideration of changes to the protocol should consider potential modifications to study conduct that will enhance safety. Those changes include decreasing the number of protocol-required trial visits at any facility at which patients with COVID-19 are seen, increasing the number of remote visits, e.g., research home visits by a nurse or study team member; telehealth and/or video-enabled visits; local blood draws and imaging; remote, technology-enabled data capture; electronic informed consent (eConsent) and providing home delivery of investigational products, among others(7-9).

While changes to study conduct may be necessary to enable the continuation or introduction of clinical trials, certain concerns with these potential changes must be addressed. Before any initiation of changes to the study protocol, consideration of confidentiality, privacy, data integrity and safety must also be addressed. Would a staff, e.g., visiting nurse home visit, compromise patient privacy or enlighten others living at home to the participant's condition? Would a home visit imperil personal safety of either the visiting staff or the participant? Is sufficient personal protective equipment available? If eConsent is suggested, can the identity of the signatory be confirmed? Can the data from remote visits be validated, especially if they depend on participant self-reports? How will source data be kept for remote visits? Lastly, are there visits that simply cannot be performed remotely due to the need to collect data from testing that cannot be conducted remotely or by home visit?(7-9).

While some risks are involved in remote visits, distinct advantages exist as well. Changes that optimize participant convenience, financial costs, and time are important and may even promote retention in the trial. No longer are participants spending significant time and effort traveling to the trial site to potentially wait in a crowded waiting room for a follow-up visit that does not require onsite medical procedures or having their blood drawn. Remote visits and data collection using certain mobile health technologies, even when part of a hybrid trial includes some in person, clinic or hospital visits interspersed with telehealth, are generally preferable to the participant and consistent with the principles of participant respect. Participants appear to appreciate the support that the visit and visiting staff member provides. Moreover, telehealth may decrease the threshold for the participant to engage outside of scheduled visits when necessary(7-9).

Research involving the deliberate infection of healthy volunteers may seem intuitively unethical, sensitive and must be carefully designed and conducted to minimize harm to volunteers and preserve public trust in research(10). In particular, investigators must adhere to standard research ethics requirements. Furthermore, research should be conducted to especially high standards where (a) studies involve exposing healthy participants to relatively high risks; (b) studies involve first-in-human interventions (including challenge)(11) or high levels of uncertainty (for example, about infection, disease and sequelae); or (c) public trust in research is particularly crucial, such as during public health emergencies(12-17).

Global public trust in research and vaccines depends on there being heightened vigilance to ensure that, the challenge studies are conducted to the highest scientific and ethical standards. Eight ethical criteria for conducting the challenge studies are set out in Table 1.

Table 1. Eight criteria for the COVID-19 pandemic challenge studies(18)

Scientific and ethical assessments		
Criterion 1	Scientific justification	The challenge studies must have strong scientific justification
Criterion 2	Assessment of risks and potential benefits	It must be reasonable to expect that the potential benefits of the challenge studies outweigh risks
Consultation and coordination		
Criterion 3	Consultation and engagement	The challenge research programs should be informed by consultation and engagement with the public as well as relevant experts and policy-makers
Criterion 4	Coordination	The challenge study research programs should involve close coordination between researchers, funders, policy-makers and regulators
Selection criteria		
Criterion 5	Site selection	The challenge studies should be situated where the research can be conducted to the highest scientific, clinical and ethical standards
Criterion 6	Participant selection	The challenge study researchers should ensure that participant selection criteria limit and minimize risk
Review and consent		
Criterion 7	Expert review	The challenge studies should be reviewed by a specialized independent committee
Criterion 8	Informed consent	The challenge studies must involve rigorous informed consent

The following list of criteria for the ethical acceptability of the challenge studies is not exhaustive, and other usual research ethics criteria and local requirements should be met.

Criterion 1: Scientific justification: The studies must have strong scientific justification where studies aim to produce results of public health importance, especially to the extent that similar results could not feasibly be obtained as efficiently or expediently in other study designs involving less risk to human participants(19, 20).

Criterion 2: Assessment of risks and potential benefits: Standard research ethics requires that, on balance, benefits should outweigh risks. Potential benefits and risks should be evaluated for each of three key groups: (a) participants; (b) society (in general) and (c) third-party contacts of participants. Regarding the systematic assessment of potential benefits and risks, and judgment that the former outweighs the latter, expected benefits should be maximized and risks should be minimized, other things being equal. For example, benefits should be maximized to the extent possible without increasing risks to participants, and risks should be minimized(21).

Criterion 3: Consultation and engagement: Activities should ideally be rapid, rigorous and mutually informative such that the views of the public and expert groups are updated considering each other. Such consultations should seek considered public views on proposed research plans with engagement techniques that enable genuine dialogue in advance, and hence without unduly delaying potentially beneficial research. Goals of public engagement should include assessing local acceptability of the challenge studies, responding to community concerns, maximizing transparency, and understanding the potential impact of research on the community (especially in light of other social and public health disruptions related to the pandemic)(22).

Criterion 4: Coordination of research: The study research programs should involve close coordination between researchers, funders, policy-makers and regulators. Research should thus be coordinated with public health agencies to avoid unduly compromising the local public health response to COVID-19, for example, during peak transmission periods(23). Studies should have adequate oversight from other relevant authorities. Study data should be shared rapidly and ideally made publicly available (with appropriate protections). Especially important data include those regarding measures of vaccine safety and efficacy, as well as any harm to participants.

Criterion 5: Site selection: The studies should be situated where the research can be conducted to the highest scientific and ethical standards. Given the urgency, risk and uncertainty involved, initial the studies should only be conducted in centers with significant experience in designing, reviewing and conducting human challenge studies. These centers should also have access to appropriate facilities in which to prepare challenge strains, and safe, comfortable isolation for participants. Centers should also ideally have experience with community engagement (see Criterion 3). There should be provision for high-quality care (including intensive care if required), long-term follow-up of participants, and full compensation for any research-related harm.

Criterion 6: Participant selection: The study researchers should ensure that participant selection criteria limit and minimize risk. The safety of participants is a key necessary condition for the ethical acceptability of the studies. Participant selection criteria must be designed to ensure a high level of confidence that participation is as safe as possible. Initial studies should thus be limited to young healthy adults(24).

Criterion 7: Expert review: The studies should be reviewed by a specialized independent committee. The studies should be the subject of specialized independent review in addition to or in conjunction with a standard local ethics review, as is the case for some other types of research that may be controversial or involve higher levels of risk and uncertainty(12). A specialized review committee should include members with relevant scientific expertise and members with research ethics expertise specific to the studies.

Criterion 8: Informed consent: The studies must involve rigorous informed consent. Informed consent processes should be particularly rigorous in the studies because of the heightened potential risks and uncertainties involved(12, 25). Consent should be revisited throughout the study, as is often the case for other studies.

Consequently, conducting research on new medications or vaccines during a pandemic is essential, and research ethics committees need to be prepared to rapidly review related research projects. To facilitate rapid, time-sensitive reviews, research ethics committees need to consider the recommendations listed below for additions or changes to existing standard operating procedures(26).

1. A checklist including the following items should be included in addition to the ethics review form (if used by the review committee)

   a. identification of the research as epidemic or outbreak related to facilitate fast-tracking

   b. description of whether prior research data about the disease exist (include references of recent local and international studies)

   c. inclusion of at least one (preferably two) principal investigators or co-principal investigators of the country where research and review are taking place

   d. qualifications of key investigators, including a description of previous track record with outbreak-relevant research among the research group

   e. an indication as to whether the protocol is part of a multi-center trial (if yes, an opportunity should be provided to describe the status of ethics approval of the master protocol or the ethics approval of the sponsoring country).

2. Apart from the usual documents submitted for review (such as protocols or (Curriculum Vitae (CVs)), the materials listed below should also be submitted.

   a. a letter of collaboration (in the form of a memorandum of understanding) with sponsor institutions and the funders of the research, along with declarations of interest when possible

   b. a monitoring and safety management plan for the project by the principal investigator and the study sponsor

   c. both data-sharing and material transfer agreements for data and human biological material, especially if samples are being exported out of the country, while honoring the laws of the land (a draft may be submitted initially)

   d. clear processes and procedures for follow-up dissemination and publication, co-authorship, co-presentation, and intellectual property rights

   e. procedures for dissemination of findings to the affected community (important to ensure maintaining contact with and upholding the trust of the affected populations, especially research participants)

   f. local requirements on insurance policies, particularly regarding trials and interventions, may also be included.

3. To prepare for the review of emergency research, research ethics committees should agree on a process for rapid review (this would mean reviewing protocols as and when they are submitted rather than waiting for a scheduled meeting). This process should be communicated to the researchers. Any anticipated delays for non-emergency research should also be communicated to all principal investigators who had previously submitted such research projects.

4. Other practical considerations include identification of the surge capacity for review, setting up systems for remote discussions, for example, which software platform, does everybody who needs it have access to it and know how to use it, what will be the back-up plan if the Internet is not functioning.

5. Pre-identifying a certain number of members who will share the major burden of review is essential. These members would require specialized training (or equivalent experience) in reviewing research in outbreaks so that they are able to rapidly review research proposals without compromising ethics considerations. Additional members should be identified and called for review at times when demand increases.

6. Once an outbreak is imminent or in progress, the chair or the secretary of the review committee should alert members and ascertain which members would be available for the rapid review.

7. Subject experts (technical) and people with strong knowledge of ethics (both in country and abroad) willing to serve as ad hoc or co-opted members during outbreaks should be identified and contacted in advance, as there is a likelihood of receiving multiple projects that need to be reviewed in a timely manner.

8. A quorum shall consist of one third of all members of the research ethics committee (pre-identified to include relevant people).

9. If a pre-identified member of the committee submits their review but is unable to join the meeting, they should be considered as part of the quorum requirement.

10. Once revised, the new standard operating procedures should be circulated to all members of the review committee.

11. The review meetings could be virtual or electronic, especially when a face-to-face meeting in a highly infectious outbreak such as COVID-19 represents a health risk to committee members.

12. Protocols should be submitted electronically to save time; a hard copy, if mandatory, can follow. Principal investigators should contact the research ethics committee as soon as possible to communicate their intention to submit a high level overview of research, for example, a trial of a new medicine or vaccine, an observational study or a survey, so that the committee is aware of protocols that may be forthcoming.

13. Face-to-face meetings with the principal investigators should not be mandatory, and when necessary electronic or virtual venues may be adopted.

14. Protocols should be sent to reviewers within 24 hours of submission.

15. Reviewers should complete their reviews within a specified period of time (usually three days is sufficient and appropriate during an outbreak).

16. The consolidated review and suggestions (or approval) should be communicated to the principal investigator within a specified period of time (usually five days).

17. Electronic or telephonic communication with principal investigators should be initiated to seek clarifications, thus saving time.

18. The principal investigator should respond to the review as soon as possible, but not later than 48 hours.

19. Focal points or persons for communication in respective national and institutional (research) ethics committees should be identified as early in the process as possible.

20. All communications should be documented and archived.

Conclusion

Conducting research in this situation is challenging to researchers. However, researchers must balance using the correctness of scientific validity and adhering to the basic principles of research ethics in operation.

Potential conflicts of interest

The author declares no conflict of interest.

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