Ethical challenges in health research during global health emergencies

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During global health emergencies such as COVID-19, healthcare leaders and researchers need to learn as much as possible as quickly as possible, to develop new therapeutics, adjust ways of caring for people and find the best way of delivering health services in a difficult situation.^{1,2}

Due to urgency, research in health emergencies presents complex ethical issues, and many ethical challenges have been highlighted during the current COVID-19 outbreak. This prompted the World Health Organization (WHO) to publish a list of key ethical guidance documents to ensure that COVID-19 health research still complies with the internationally accepted norms of basic ethical principles such as respect for persons, beneficence and justice. The aim of this article is to identify ways to address some of the ethical challenges encountered in emergency situations by way of the above ethical guidance documents.^{2,3}

The need to accelerate knowledge

During global health emergencies, the most important duty of healthcare leaders is to respond to the needs of those affected, without impacting negatively on the importance of conducting health research to prevent or alleviate disease outbreaks.⁴ The process for developing treatment and vaccines is lengthy and it takes many years to develop safe and effective treatments or vaccines. Normally, interventions that show promise undergo testing in extensive clinical trials to generate reliable evidence about the safety and efficacy of the intervention.⁵ However, health emergencies call for accelerated development and access to lifesaving products. Speeding up research timelines may lead to faster access to potential therapeutics, but participant safety, ethical principles and quality data remain vital during research and should not be overshadowed by the need to attain knowledge. A risk of fast-tracked research and development is that potential research participants may consider any conceivable intervention better than nothing and be willing to participate in research without weighing up the risks and benefits and making informed decisions.³ Therefore, measures must be put in place to guarantee that patient safety is not compromised regardless of the urgent need for knowledge.

The need to accelerate knowledge may also urge regulators to allow the use of registered treatments off-label (based on preliminary data) before they are approved for use in COVID-19.

This will not only result in safety and efficacy concerns in COVID-19 patients but may also lead to reduced availability of the products for those indications in which the treatment is proven to be effective.⁶

A potential measure to accelerate research without compromising patient safety and data quality is to coordinate national and international research projects and avoid needless repetition by integrating research into broader outbreak response endeavours. By coordinating research efforts, research sponsors and host countries can agree in advance that positive outcomes will be communicated to local populations without delay and products found to be safe and effective can be made available for compassionate use before regulatory approval.²

Furthermore, in global health emergencies it can be ethical to offer individual patients investigational interventions on an emergency basis outside clinical trials. The WHO developed an ethical framework known as Monitored Emergency Use of Unregistered Interventions (MEURI) which established the following criteria to access investigational therapeutics for individuals outside clinical trials in the following instances: 1) no proven effective treatment exists; 2) it is not possible to initiate clinical studies immediately; 3) preliminary data (laboratory and animal studies) of efficacy and safety are available and the use of the interventions outside clinical trials is supported by a qualified scientific advisory committee based on a favourable risk-benefit analysis; 4) local regulatory authorities as well as a registered health research ethics committee have approved such use; 5) patient's informed consent is obtained; and 6) the emergency use is monitored and the results are documented and shared with the medical and scientific community in a timely manner.⁵

In spite of the above measures and exceptions, those responsible for research design and approval during global health emergencies must not forget their moral obligations to guarantee that no therapeutic is given or clinical trial is started without confirming patient safety, scientifically valid research, meaningful participant engagement and voluntary informed consent.¹

Upholding public trust

Public trust during the process of COVID-19 health research design and implementation plays a fundamental role in safeguarding commitment and interaction of affected communities. If

researchers interact with the public to determine concerns and expectations in the early stages of research, it may assist with study recruitment and completion and may also bolster uptake of interventions proven to be efficacious.² Trust of the potential participant in the system and in the researchers is essential during the decision-making process. This is especially important where the public's trust in government is fragile or where public opinion and trust in health care may be influenced by COVID-19-related fears. Ethical values such as respect and fairness will go a long way towards upholding the trust of communities and research participants.

Early public engagement, during which the local needs of the research participants and communities are recognised, is a key factor for successful research as it shows respect for the communities in which the research is to be conducted. These needs include recognition of local traditions and languages, communication with communities and local consultants, a humanitarian approach to clinical research and feedback on study findings.¹ Without community engagement, research is unlikely to have any lasting impact and is unlikely to inspire policy making.

There is an ethical duty on healthcare leaders responding to COVID-19 to promote public safety, protect community health, and allocate limited resources in a fair manner. During public health emergencies, the community must be prioritised above the individual in fairly assigning limited resources.⁴ Fair treatment of research participants and communities requires fair benefits from the conduct and/or the results of the research as well as fair distribution of interventions found to be safe and effective. The process of distribution of benefits must be communicated to all parties involved in the research and must be transparent.

Furthermore, once COVID-19 therapeutics are available, limited quantities will be accessible due to global need. With this demand come the questions of who will be prioritised and how can we guarantee this distribution will be fair? Consequently, it is extremely important for governments, researchers and other healthcare leaders to be transparent regarding the prioritisation policies for providing treatments or vaccines and to raise public awareness of why certain sub-groups of populations (e.g. healthcare workers, the elderly and immune-compromised individuals) may be prioritised in the event of inadequate supplies.⁶ Without transparency about the distribution of benefits to research participants or communities, resentment, mistrust and a sense of exploitation will be generated.⁷

Scientifically valid research

Science and ethics do not contradict. Unscientific research is *ipso facto* unethical research. Research study designs in health emergencies must be achievable without influencing scientific validity and social value of the research. Researchers and sponsors may be forced to deviate from the typical 'randomised-controlled' or 'placebo-controlled' study design to increase efficacy and accelerate access but it remains ethically unacceptable to expose research participants to potentially risky

research if useful research results are improbable and reliable and valid data cannot be generated.⁴

Research proposals must be developed with attention to both the scientific validity of the data and feedback from communities to ensure the study design is appropriate for the community from which participants will be drawn and will benefit the community.² Selection criteria must be justified in relation to the risks and benefits of the research populations and ensure that vulnerable populations (e.g. elderly, minors, illiterate) are not excluded from low-risk, potentially beneficial treatment or exposed to high-risk research simply because they are vulnerable.¹ Possible risks and benefits must be distributed equally in the communities in which the research will be conducted.

In addition, research must be designed in such a way that the results will address a health problem in the research community and obtain the research objectives without denying healthcare services that participants are entitled to, or requiring services that are not possible within the country's healthcare system. The research must also be designed to be feasible within the cultural, social, and political setting in which the research is conducted.⁷

Flexible ethical review and oversight

Independent ethical review of health research offers an essential safety net to research participants, ensures public accountability and addresses concerns about researchers' conflicts of interest.⁷ Nevertheless, normal timeframes and procedural requirements for independent ethics review may delay approvals and have a negative impact on health research during global health emergencies. This does not imply that the standards of research should be compromised, but that consideration should be given to altering review processes and timelines to support expedited or rapid ethics review in emergency situations.¹ During health emergencies, National Health Authorities, researchers, and Health Research Ethics Committees (HRECs) should put mechanisms in place to ensure rapid ethics review without compromising the ethical standards and protections offered by independent ethical review.²

Various options can and should be considered to this effect. Generic protocols for conducting health research in emergency situations can be approved in advance and then rapidly modified and reviewed for specific contexts.² Extremely urgent applications can be fast-tracked by implementing expedited review timelines and flexible means of communication between researchers and HRECs (e.g. online submissions, feedback, and approvals), and HRECs can conduct initial fast-tracked reviews with continued review and oversight of ethical concerns once the research is approved.^{1,4}

In some developing countries, the capacity to conduct local ethics review may be inadequate due to lack of infrastructure of HRECs, time restrictions, lack of expertise or pressure from public health authorities that may influence independent review.² To accost these concerns and prevent unnecessary duplication of ethics review and oversight, consideration should be given to collaborative independent ethics review between local and

international HRECs, with at least one of these committees being knowledgeable in research ethics.³

Informed consent

Personal informed consent from research participants is one of the essential principles of ethical research, but it can be incredibly challenging in developing countries due to language barriers, illiteracy, vulnerability and social traditions and practices. This makes the process to obtain fully informed consent even in non-emergency settings overly complex.⁷ In global health emergencies, the addition of fear and desperation can prove even more challenging. In desperation, any conceivable treatment or vaccine may be considered better than nothing regardless of the potential risks and inconvenience. Potential participants may also be predisposed to therapeutic misconception, believing that the investigational intervention is predominantly developed to directly benefit the individual participant rather than potentially benefitting society. Furthermore, factors such as disruption from daily routine, quarantine and isolation, family separation and lack of basic needs, may further contribute to challenges in obtaining informed consent as participants may feel incapable to decline participation.²

The process for obtaining informed consent in global health emergencies must be planned in a way that is sensitive to the above challenges and ensures fully informed and voluntary informed consent from research participants.⁴ This can be done in various ways. First, the process for obtaining informed consent must be developed in consultation with local communities and researcher to guarantee culturally appropriate and respectful consent processes.⁷ Second, imaginative ways to present complex scientific information, verify comprehension and avoid stigma must be utilised by providing informed consent documents in local languages with consideration to social traditions and different levels of literacy. Participants must be provided with useful tools such as videos, pictures, flowcharts, and brochures to simplify research procedures and make it applicable to their daily lives. Third, researchers must be aware of the medical, psychological, and social support systems available to participants who may be in need for these services during their participation and make potential participants aware of the services during the informed consent discussion.³ Lastly, specific attention must be given to confirm that research participants are

aware that their participation is completely voluntary and that they have the right to refuse participation or withdraw from the research at any time without providing a reason and without it affecting their future medical care.⁷

Conclusion

The COVID-19 pandemic has disrupted everyday moral assumptions. There is still too much we do not know about COVID-19 and the longer we take to gain this knowledge, the more lives will be lost. Responding to a global health emergency involves collaboration between various organisations and will unavoidably lead to conflict because of variation in approach. However, it is of the essence to remember that ethics and ethical research do not only include the people directly involved in the research but also the decisions made by policy makers, funders, regulators, review boards, research institutions, etc. Collaboration between all parties will ensure that health research is undertaken ethically during emergencies to find the best way of conducting meaningful health research during incredibly challenging situations.¹

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