



EPIDEMICS ETHICS

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Ethical Conditions for Accelerating COVID-19 Vaccine Research

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Abstract: There is a dire need to produce a safe and effective COVID-19 vaccine as quickly as possible to avert an enormous burden of morbidity and mortality. This need for speed has thus far resulted in significant deviations from standard approaches to vaccine research and regulatory approval. Yet, pandemics do not obviate the need for rigorous scientific evaluation of potential interventions and adherence to universal ethical standards. Consequently, steps taken to accelerate clinical research in the context of the current pandemic require an explicit ethical justification, particularly if we expect public trust in the vaccine. We argue that accelerating COVID-19 vaccine research can be ethically justified, but only if social value, scientific validity, and a favourable risk-benefit ratio can be maintained or enhanced when doing so.

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INTRODUCTION

There is a dire need to produce a safe and effective COVID-19 vaccine as quickly as possible to avert an enormous burden of morbidity and mortality. This need for speed has thus far resulted in significant deviations from standard approaches to vaccine research and regulatory approval. For instance, Russia, China, and the United Arab Emirates have each authorized COVID-19 vaccination outside of clinical trials,^{1,2,3} and the US Food and Drug Administration has expressed its willingness to consider granting emergency authorization for a COVID-19 vaccine before phase three trials are completed.⁴ In addition, the World Health Organization (WHO), via the COVAX pillar of its Access to COVID-19 Tools (ACT) Accelerator, is coordinating a global approach to the acceleration of COVID-19 vaccine R&D.⁵ The WHO's protocol for its 'Solidary Vaccine Trial' calls for only some of its trial sites to perform detailed safety assessments in each treatment arm (as typically done in phase two trials), where other study sites will proceed directly to phase three testing following the review of early safety assessments of vaccine candidates.⁶

Accelerating the evaluation and development of vaccines is not without precedent. Some phase two enrolment began in the absence of published phase one data during Ebola vaccine trials.⁷ In addition, given the large number of people affected by the 2013-2016 Ebola outbreak and a high case-fatality rate, a WHO advisory panel argued on both ethical and evidential grounds that it was permissible to use unregistered interventions that have shown promising results in laboratory and animal models as potential treatments or for prevention, provided that certain ethical and scientific criteria were met.⁸

Despite the need for speed, pandemics do not obviate the need for rigorous scientific evaluation of potential interventions and adherence to universal ethical standards.⁹ Consequently, steps taken to accelerate clinical research in the context of the current pandemic require an explicit ethical justification, particularly if we expect public trust in the vaccine. We argue that accelerating COVID-19 vaccine research can be ethically justified, but only if social value, scientific validity, and a favourable risk-benefit ratio can be maintained or enhanced when doing so.

SOCIAL VALUE

For research involving human participants to be ethical, it must have social value.¹⁰ It is clear that COVID-19 vaccine research has social value insofar as the development of a COVID-19 vaccine has the capacity to avert substantial morbidity and mortality worldwide.

But would social value be maintained or enhanced by deviating from the standard approach to clinical research and accelerating COVID-19 vaccine research? The virus is rapidly infecting the global population. Nearly one million people have already died. The more time that elapses between now and a vaccine, the more people will become ill and die. Moreover, no vaccine or therapy currently exists for this disease, making this research of even greater social value. Finally, the high social value of accelerated research in this context is symbolized by the fact that it responds to a threat for which a public health emergency of international concern has been declared.¹¹ Given the substantial social value that a COVID-19 vaccine promises, there is an ethical imperative to proceed more rapidly.

However, social value may be diminished when studies are of low quality, research is unnecessarily duplicated, and data are not shared—concerns which may be particularly relevant for research conducted during pandemics.¹² Social value can be enhanced in this context via core protocols with adaptive designs, such as that proposed for the Solidarity Vaccine Trial, which promote collaboration and permit adding, dropping, and assessing multiple interventions under a common evaluative framework.

SCIENTIFIC VALIDITY

Research must be conducted in a scientifically rigorous manner if it is to be ethical.¹⁰ Consequently, even where the prospect of social value is high, any steps taken to accelerate COVID-19 vaccine research must be scientifically valid to avoid scientifically unreliable results.

Assessing the scientific validity of accelerating vaccine research by combining or skipping trial phases should be situated within a broader understanding of the reasons for a phased approach to clinical research. The phases of clinical research reflect a general schema that scientists follow to obtain valid and rigorous scientific data about the safety and effectiveness of investigational products. What is important is not the phases *per se*. They are merely a means to an end. Large-scale phase three testing has the capacity to generate sufficiently rigorous scientific safety and efficacy data. But proceeding with phase three testing in the absence of sufficient prior safety data has the potential to put participants at risk, and proceeding in the absence of sufficient efficacy data could be a waste of time and resources if it turns out the vaccine is not efficacious. Consequently, what is primarily at stake when accelerating research in this way isn't scientific validity, but rather a favourable risk-benefit ratio.

FAVOURABLE RISK-BENEFIT RATIO

Research entails uncertainty about the degree of risks and benefits.¹⁰ Typically, risks and benefits are balanced in clinical research by only increasing the number of individuals exposed to an investigational product as uncertainty is reduced regarding the product's risk-benefit ratio, as it generally does as we move through phases one, two, and three.

Consequently, the possibility exists that accelerating vaccine research would mean exposing a greater number of participants to an investigational product before a sufficient degree of certainty can be generated about the product's safety or efficacy. A justificatory condition for accelerating COVID-19 vaccine research is therefore the degree to which sufficient safety and efficacy signals are capable of being generated before large numbers of participants (or populations, in the case of regulatory approval) are exposed to the investigational product. So long as there is sufficient evidence of low risk and some chance of benefit in terms of potential protection against COVID-19, then accelerating the research approach would be justifiable.

To enhance the scientific rigour and ethical justification of this approach, several conditions should be fulfilled. Monitoring and oversight of safety by an independent data monitoring committee during all research phases should be enhanced. The data monitoring committee should review data sooner and more frequently and stopping rules should be stricter in order to quickly capture safety signals. Where possible, investigators should consider safety results from earlier phases when designing safety monitoring plans. The trial should not proceed in locales where this sort of monitoring is not possible. Finally, it will be important that phase three testing be followed up with robust post-trial surveillance that includes active monitoring for adverse

effects, especially where phase three trials are not adequately powered to detect rare adverse events.

CONCLUSION

Finding ways to speed up research to produce a COVID-19 vaccine is an attractive prospect. Yet, the fact that we are in a pandemic does not provide sufficient warrant to lower our scientific or ethical standards.¹² Steps taken to accelerate COVID-19 vaccine research must therefore be subjected to rigorous scientific evaluation and adhere to universal ethical standards. This requires that steps taken to accelerate COVID-19 vaccine research maintain or enhance social value, scientific validity, and a favourable risk-benefit ratio. Any deviation from the standard approach to research should be explicitly justified in scientific and ethical terms, and this justification should be communicated transparently to researchers, review committees, research participants, and the public in order to engender trust in this research and the vaccine we hope it produces.

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