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PERSPECTIVE

Pandemic Pandemonium

Pausing Clinical Research During the COVID-19 Outbreak

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Ethicists and researchers have written about concerns unique to conducting clinical research on pandemics. Less guidance is available, however, about conducting unrelated clinical research during a pandemic. On what grounds should we pause or continue studies that do not shed direct light on the pandemic? In the United States, most clinical research is subject to review by an institutional review board, which applies federal regulations known as the Common Rule that, in turn, reflect the ethical principles developed in the Belmont Report. An institutional review board may approve a study only if it finds that risks to participants are reasonable in relation to the expected benefits to them, if any, plus the expected benefit to society in the form of knowledge production. After a study has been approved, intervening events that change that risk–benefit balance can change the acceptability of the study.

There are reasons, in light of that framework, to pause or end some clinical research (Figure). In particular, investigators, institutional review boards, and organizational leadership should consider whether a study now poses increased risks to participants, researchers, or bystanders. In-person research procedures may undermine critical public health measures such as social distancing, which are especially important in healthcare settings. Clinical research is often conducted at academic medical centers, facilities that treat many critically ill patients. Participants who are infected and travel to healthcare settings for research procedures might spread the virus among a community's most vulnerable members who are seeking medical care and cannot feasibly choose to practice social distancing. Although one of the Common Rule's moral blind spots is that it does not consider risks to either third parties or researchers, broader ethical principles require that we consider their interests when deciding whether to pause research during a pandemic.

The study protocol itself might place participants at risk if they become ill. Beyond obvious examples, such as the study of immune-modulating drugs to treat non–life-threatening conditions, other studies might also need to be paused for this reason. One of the authors (J.B.B.) is performing a study that involves administration of very high-sodium and low-sodium diets. It is unknown whether coronavirus disease 2019 (COVID-19) might be poorly tolerated by people on these diets. In addition, the supply chain of materials is in question. For these reasons, the need for social distancing, and the lack of potential benefit to participants, he has paused study visits.

On the other side of the risk–benefit ledger, disruptions caused by the pandemic may reduce data quality, with the result that risks assumed by participants would no longer be balanced by sufficient social benefit in the form of knowledge production. A growing number of clinical trials are multinational. Results may be skewed if the study is not implemented as planned because of changing resource allocation from research to clinical care at some but not all study sites. Study

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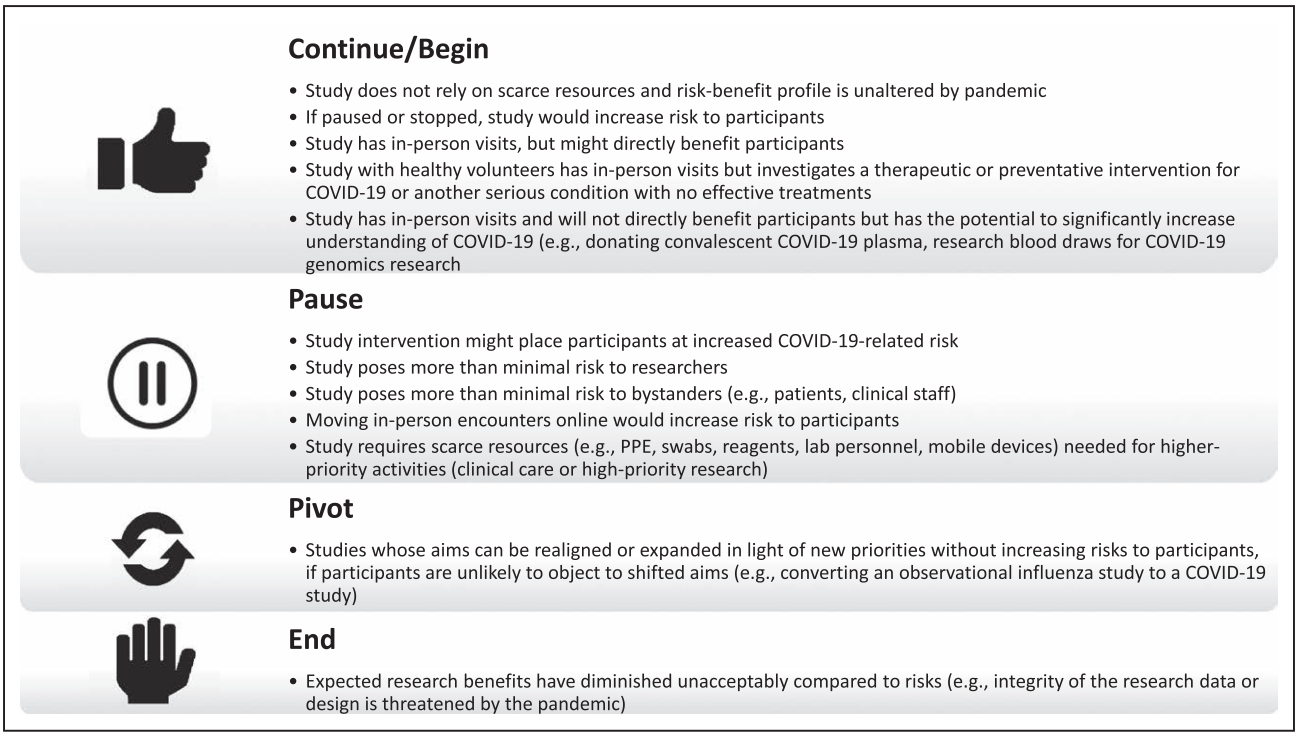

Figure. Considerations relevant to clinical research pauses during a pandemic.
The figure describes considerations relevant to whether research should continue or start, pause, pivot to focus on the pandemic, or end. COVID-19 indicates coronavirus disease 2019; and PPE, personal protective equipment.

participants might avoid academic medical centers and other clinical research institutions during the pandemic, causing protocol deviations that will be avoidable after the pandemic has receded.

Other research should be paused not because the pandemic alters the study's risk–benefit ratio but because scarce resources devoted to those studies (eg, skilled personnel, swabs, reagents, mobile devices) are better allocated elsewhere, whether to COVID-19 research or to clinical care.

The same risk–benefit framework suggests that other studies unrelated to the pandemic should continue. For example, the pandemic is unlikely to affect the risk–benefit profile of research conducted entirely online. In other cases, pausing research could cause more harm than good. Canceling study visits abruptly could endanger participants in studies requiring safety checks.[1] If a pause causes the study to fail—for example, because of cost overruns—then any risks or burdens already undertaken by participants might cease to be balanced by societal benefits. Even during a pandemic, other threats to morbidity and mortality remain. Pausing therapeutic trials, which may provide direct benefit to participants, is unlikely to be warranted. Even nontherapeutic studies that advance our understanding of serious conditions may be justifiably continued. Many life-threatening diseases remain fundamentally poorly understood, and a delayed breakthrough will come too late for some patients. Continued studies should have contingency plans in case the evolving pandemic causes interrupted visits, incomplete data collection, and supply chain interruptions. A study drug may become unavailable during the course of a clinical trial, and a plan must be in place to address this possibility.

Rarely, ongoing research should neither pause nor continue as usual but pivot to address the pandemic.[2] An HIV research network was adapted to study the 2009 influenza pandemic.[3] In such cases, thoughtful interpretation of research regulations and ethics is critical. Researchers leading the Seattle Flu Study wanted to test existing samples for COVID-19 to help define the size of the outbreak in the state but were reportedly stymied by regulators who maintained that explicit consent from participants to test for COVID-19 was necessary, as was testing in a laboratory certified by the CLIA (Clinical Laboratory Improvement Amendments of 1988). Although consent terms generally must be respected, those that were included reflexively and that were likely unimportant in participants' decision to enroll in the study should not be dogmatically adhered to when overriding them does not significantly increase participant risk and could substantially benefit society or participants themselves.[4] Although Centers for Medicare and Medicaid Services regulations prohibit non-CLIA laboratories from returning individual results for the purpose of diagnosis, it is a myth—which can become tragic during a pandemic—that they prohibit

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return of results for other purposes, including to provide research participants notice that they might be at risk and should consider clinical testing.[5]

In these circumstances, clinical researchers will be faced with challenges and will need to make difficult decisions. When research is paused, there will be human costs to trainees and technicians whose careers and families depend on these positions. As has been done in Seattle, we should find novel ways to divert this talent pool and put their skills to use in other ways that aid humanity, without subjecting to them to COVID-19–related risks.

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