Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COMMENTARY

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Navigating Conflicting Interests in Pandemic Research: Preparing the US Research Infrastructure for a Worse Pandemic

During the coronavirus disease 2019 (COVID-19) pandemic, some research systems operated efficiently and achieved great things, such as rapid development of RNA vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). At the same time, this pandemic has exposed weaknesses in these systems, requiring a fundamental re-examination of how we will conduct research during the next public health crisis. The COVID-19 pandemic has caused immense physical, psychological, and economic harms. However, future pandemics could be much worse with even a slightly higher case fatality rate. Despite nearly 3 years of experience with COVID-19, the 2021 Global Health Security Index concluded that "no country is fully prepared for future pandemic or epidemic threats."[1] Readying for the next pandemic must include not only emergency preparedness and response, but also efficient and collaborative research processes that can adapt to an emerging infectious threat.[2]

Our group surveyed 211 COVID-19 researchers and 143 institutional review board leaders during the early months of the pandemic in the United States to identify ethical, regulatory, and logistical barriers to performing research on COVID-19, with full results published elsewhere.[3] From this study and review of the literature, we found that COVID-19 research collaboration and productivity was stymied by conflicting interests related to accessing patients, data, and investigational drugs for research. In a future pandemic, these unresolved conflicts could impede essential research and lead to even greater societal harms. Addressing these conflicting interests could require radical, unprecedented actions by the federal government. Below, we describe these interconnected webs of conflicting interests, and we propose strategies that might mitigate these conflicts.

ACCESS TO PATIENTS

Many researchers were unable to enroll sufficient participants with COVID-19 due to large numbers of trials launching within their health care systems. Institutions commonly responded by establishing COVID-19 protocol review committees that approved and prioritized studies. While necessary, researchers described delays, bias, and lack of transparent, uniform procedures for protocol review or determination of a study's priority. While multicentered trials were the ideal, many researchers were denied access to existing multicenter trials, despite best efforts, for seemingly arbitrary reasons.[4] Researchers also struggled to engage nonacademic research organizations in recruitment efforts, with some Health Departments perceiving recruitment efforts of clinical trialists to be "unethical."[3] Researchers decried the lack of national leadership for conducting multicenter trials and addressing conflicts over access to patients, which led to competition rather than cooperation.

To address conflicts over access to patients, the National Institutes of Health (NIH) could develop centralized protocols and associated funding for high-priority trials. For example, if a site demonstrates capacity to perform these studies and recruit sufficient patients, they could join these clinical trials and access government funding. These centralized clinical trials could decrease conflicts over accessing relatively small patient populations by concentrating efforts on fewer, larger studies that span multiple institutions. Early stopping rules could be used to expand the

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number of trials conducted in succession. Emergency rules could be instated for highly infectious, deadly diseases.

ACCESS TO DATA

Researchers experienced bureaucratic and logistical issues that impeded the sharing of data and materials across centers, especially related to material transfer agreements, data use agreements, and intellectual property considerations. These proprietary and financial conflicts delayed research studies, and in some cases led to termination of ongoing clinical trials, even after collection of data. Barriers to developing collaborative databases and biorepositories led to similar challenges, with multiple parallel COVID-19 registries existing with overlapping information, rather than shared registries that provided broad access.

At the other end of the spectrum, the desire to quickly share even the most preliminary findings led to challenges with expedited publication of inaccurate or untrustworthy results. The urgent need for data led to enormous numbers of COVID-19-related manuscripts submitted to academic journals. One group performed a Medline search for COVID-19-related studies in May 2020 (5 months after the first US case of COVID-19), identifying more than 15,500 articles.[5] This plethora of publications did not provide clarity or definite answers. Studies often were poorly designed, observational, anecdotal, and written in short format.[5] Furthermore, journals had difficulty finding qualified reviewers, leading to reviewers with limited expertise or conflicts of interest.[6]

To mitigate conflicts over data access, the US Food and Drug Administration (FDA), NIH, and other government agencies could mandate that participation in prioritized clinical trials—and even future FDA approval of drugs and devices—require compliance with material transfer agreements, data use agreements, and data sharing requirements that prioritize benefit to public health over intellectual property rights when conducting research on a deadly pandemic. Funding research that adopts centralized protocols could incentivize participation in clinical trials while bypassing contentious, time-consuming, and restrictive negotiations between organizations about data ownership and intellectual property.

ACCESS TO DRUGS

Given the urgency to find treatments for COVID-19, most studies of treatments repurposed existing medications that were previously used for other indications. Simultaneously, many clinicians trialed these unproven treatments as part of clinical practice. When case reports and anecdotal experiences suggested the efficacy of certain medications in treating COVID-19, media reports and political commentary overstated the impact of these drugs, increasing demand for these unproven treatments. This created drug shortages that affected COVID-19 clinical trials, as well as patients who needed the medications for other indications. One group of researchers described their intense effort to design and implement a clinical trial, only to learn that drugs were not available.[7]

Cost was another barrier to accessing drugs for clinical trials. Many single-center studies were unfunded or self-funded by academic institutions. Without sponsorships, institutions paid for drugs used in studies, and this practice is unsustainable. When physicians prescribed the same drugs outside of clinical trials, they billed insurance. While certain drugs were inexpensive, others created financial stresses and pressure from institutions to limit use of these drugs. This lack of access and affordability of drugs exacerbated barriers to participating in multicenter studies, which limited the feasibility of trials, the scope of available experimental agents, and the utility of results.

To combat drug shortages, the federal government might collaborate with pharmaceutical companies to overcome supply chain issues and develop strategies for rapid escalation of production in the future. Furthermore, the government might negotiate discounted rates for clinical trials that could benefit these companies if these trials lead to new FDA-approved indications. Alternatively, the government could leverage emergency powers to increase manufacturing of drugs in short supply.

PREPARING THE US RESEARCH INFRASTRUCTURE FOR A WORSE EMERGENCY

The COVID-19 pandemic exposed significant shortcomings in the US research infrastructure that will impede responses to future emergencies. Conflicting interests hampered access to every essential element of clinical research: patients, data, and investigational drugs. Addressing these conflicting interests could require radical, unprecedented actions by the federal government. We urgently need criteria for triggering emergency research protocols, and equally important, criteria for ending the use of such protocols.

We urge the development of a national working group—representing those with relevant expertise and conflicting interests—to develop actionable strategies to mitigate these conflicts. Participants in this working group might include the Association of American Medical Colleges, Department of Health and Human Services, FDA, the National Academy of Medicine, NIH, Pharmaceutical Research and Manufacturers of America, Public Responsibility in Medicine and Research, and cloud-based technology companies. If we do not take steps to address these issues now, we might fail the test of the next public health emergency.

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