Emerging Lessons From COVID-19 for the US Clinical Research Enterprise
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In this issue of JAMA, Janiaud et al1 present a meta-analysis of randomized clinical trials (RCTs) of convalescent plasma for the treatment of patients with COVID-19. Based on an analysis of 1060 patients from 4 RCTs published in peer-reviewed journals and 10 722 patients from 6 RCTs (5 published as preprints and 1 as a press release), the authors found that treatment with convalescent plasma vs placebo or standard of care was not associated with a significant decrease in all-cause mortality (risk ratio, 0.93 [95% CI, 0.63-1.38] for the 4 peer-reviewed RCTs; risk ratio, 1.02 [95% CI, 0.92-1.12] for all 10 RCTs) or with benefit for other clinical outcomes, including length of hospital stay, mechanical ventilation use, and clinical improvement or deterioration.

In August 2020, the US Food and Drug Administration (FDA) granted an Emergency Use Authorization for convalescent plasma based on observational data. Even though more than 100 000 patients have been treated in the US with convalescent plasma, none of the RCTs in the meta-analysis by Janiaud et al1 were conducted in the US.

Challenges for COVID-19 Research in the US
The great scientific achievement of 2020 was the development, testing, and approval of numerous vaccines in less than 1 year.2 The US had a major role in this effort, both regarding the basic science discoveries and the conduct of clinical trials. However, the conduct of RCTs testing treatments for COVID-19 has been more challenging. Of the nearly 30 million individuals who have developed COVID-19 in the US, only a few thousand have participated in RCTs. The US is not alone. Other than a few exceptions, most notably the UK, many countries enrolled only a small fraction of patients with COVID-19 in RCTs. Given the number of patients with COVID-19 in the US, the available resources, the number of major academic research centers, and the pressing need to have rapid, actionable evidence on optimal treatment, the US surely should have done better.

The problem is not lack of intent, effort, or resources. Hundreds of RCTs were designed and registered. Anecdotally, virtually every academic medical center in the US committed to enroll patients with COVID-19 in clinical trials. Similarly, multiple multi-institutional clinical trial networks quickly mobilized to develop study protocols, seek funding and regulatory approval, and launch enrollment. Funding was made available from several governmental agencies, including Operation Warp Speed, the National Institutes of Health (NIH), the Patient-Centered Outcomes Research Institute, and the Biomedical Advanced Research and Development Authority. Similarly, many nonprofit foundations provided support, and many pharmaceutical companies both funded their own clinical trials and provided funding or drug supplies for investigator-initiated trials. In addition, the FDA and institutional review boards across the US offered accelerated review and support of modifications to existing procedures to accommodate the challenges of conducting research during a pandemic.

The main challenges appear to be (1) the structure of the clinical research enterprise and (2) the interface between clinical research and clinical care. In the US, the clinical research enterprise is set up like a marketplace, with researchers competing against each other using the appeal of their ideas, their reputation, and their experience to convince funders and colleagues to support and recruit patients. Trials are difficult to execute, and thus become zero-sum games in that if a study team sets up a trial to answer one question, oftentimes there is little ability to support a second trial. Oversight of clinical research enterprise is limited to the ethics, safety, and scientific rigor of individual trials. There is no oversight to ensure that research questions are prioritized. Individual funding bodies may set priorities, but these bodies are largely autonomous. The argument in favor of this system is the hope that a market fosters meritocracy, something that resonates with US values. But a system that rewards investigators for championing their ideas to the exclusion of others, with no national prioritization, regardless of its merits during normal times, is neither efficient during a pandemic nor aligned with the principle of public goods (knowledge about what works to treat COVID-19 is arguably the ultimate public good).

The problems of poor coordination, limited incentives for collaboration, and lack of prioritization that arise from this minimally regulated market-based system were immediately evident. The NIH and Operation Warp Speed created the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) program to set priorities, design trials, foster collaboration and coordination across clinical trial networks, and move quickly.3 However, the structure of the US clinical

References
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research enterprise is vast and has never functioned as a single national coordinated system. The ACTIV program has done an admirable job of engaging many investigators, and although many investigators have helped with the program, most clinical research in the US lies outside the program. Moreover, within the ACTIV program, each investigator network brings its own culture, methods, and operational features. Every decision made within the ACTIV program requires agreement among numerous investigators, many of whom may have no prior experience working together. Furthermore, all COVID-19-related research still must navigate through the same regulatory and contracting hurdles that often slow the pace of clinical research. Although these hurdles have been adjusted, the number of staff working in the thousands of contracting and regulatory oversight offices around the country has remained fixed even as the communication and coordination needs have expanded.

The second challenge is the interface between clinical research and clinical care. Just as no single person, agency, or entity oversees the clinical research enterprise, no single person, agency, or entity oversees ensuring integrated coordination between research and care. Thus, throughout the US, local investigators, armed with a particular study protocol, must try to persuade their clinical colleagues to refer or help enroll patients in their trial. The clinical care team may see the logistical challenges associated with execution of the study as distracting and counter to the priorities and tasks that clinical care requires. Although researchers might argue that clinicians faced with therapeutic uncertainty should be motivated to facilitate patient enrollment in an RCT, such an argument can be overly simplistic. A clinician may wish there were less uncertainty, but nonetheless feel the choice of research or care is binary, with the duty to care prevailing.

Lessons From COVID-19 Research in the UK

One country that has demonstrated success in the conduct of COVID-19 treatment trials is the UK. There appear to be several reasons. First, societal attitudes regarding community participation and the trade-offs between community and individual goals are likely different from the US and more suited to a concerted group effort.

Second, clinicians and health care administrators all work for a single payer and delivery system, the National Health Service (NHS), with potentially fewer financial disincentives to facilitate research. The role and importance of the NHS in the UK reinforces alignment of patients, clinicians, and administrators around common societal goals.

Third, the UK government had already taken key steps to facilitate clinical research. More than a decade ago, the major government clinical research organization, the National Institute for Health Research (NIHR), coordinated with the NHS to establish the Clinical Research Network (CRN), which provides direct funds and support to NHS hospitals of all sizes (academic and community) for participation in clinical trials. This coordination was easier than might be possible elsewhere because the NHS and the NIHR report to the Department of Health and Social Care. This NIHR CRN support is only available for trials prioritized by national oversight committees. For any prioritized trial, funds flow directly to hospitals to incentivize participation and offset costs. Because these funds are contingent on enrollment numbers, hospitals not only want to participate, but want to put in place systems that garner maximum patient enrollment. Other steps taken previously to facilitate clinical research included establishing a national Health Research Authority to reduce operational burden of clinical research, providing a national regulatory framework for clinical research, and creating digital and information technology infrastructure to facilitate trials.

Fourth, operating as 1 integrated health care delivery and research organization, all beholden to a single government department, it was possible for the leadership to create and disseminate pandemic response priorities. Examples include a letter in April 2020 from the chief medical officers of Scotland, Northern Ireland, Wales, and England to every hospital in the country making clear that the clinical and research priority would be enrollment in 3 adaptive platform trials across community, hospital ward, and intensive care unit settings.5 This letter was accompanied by a leveraging of the existing NIHR CRN for site payments. An Urgent Public Health committee was set up to prioritize studies for the NIHR CRN based on the underpinning science, relevance, and feasibility during the pandemic and to avoid interference with other prioritized studies.

The UK still encountered many of the same generic challenges as the US in that academic researchers and centers have similar market-based competition, there is still bureaucracy, and many resources were overwhelmed by the sheer volume of COVID-19 cases. Notably, COVID-19-related deaths per million population are similar in the US and UK (approximately 1500 and 1700 deaths per million, respectively).6 Nonetheless, the UK was able to achieve success with respect to clinical research in that tens of thousands of patients have been enrolled in RCTs. Between the Randomized Evaluation of COVID-19 Therapy (RECOVERY) platform trial (>37 000 patients) and the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) (>5600 patients; which although an international trial has had high enrollment in the UK), robust evidence has been generated on the benefits of corticosteroids, IL-6 receptor antagonists, and anticoagulation as well as convincing data on a lack of benefit for convalescent plasma, hydroxychloroquine, and lopinavir-ritonavir.

Approaches to Facilitate Clinical Research in the US

Given the enormous biomedical resources in the US, what approaches could facilitate a more effective approach to mounting clinical trials quickly and efficiently? The US remains a distributed (and fragmented) care delivery and clinical research system, and developing a quick US version of the centralized operation used in the UK is unlikely. However, several key lessons could be applied. First, more effective and well-thought-out planning is necessary. If clinical, research, and regulatory organizations are to remain independent, with their relations governed by complex contractual and regulatory rules, there must be a nationwide investment in the development and dissemination of the
procedures by which rules are modified in an emergency. Second, structures and initiatives that facilitate clinical research should be adopted, not just during a pandemic but during all periods. The 3 priority areas include the following.

1. Implement a US Version of the NIHR CRN Hospital Payment System for Trial Participation
A US version the NIHR CRN hospital payment system for trial participation could be implemented via standing agreements between the US government and sites for participation in trials that align with national priorities, potentially administered by the US Centers for Medicare & Medicaid Services. It is crucial that the health care delivery system (and clinical care) adopts the contribution to research as a core value and is rewarded via a mechanism that is independent of any research project or investigator.

2. Prioritize the Funding and Execution of Trials That Can Be Conducted Everywhere
Well-resourced academic medical centers have allowed researchers to develop increasingly complex study protocols. There is not enough attention given to simple trials that can scale easily across numerous environments at low cost. Even though randomization, informed consent, and safety remain critically important, there is arguably no other design feature that need be held essential. Unnecessary complexity can be devastating to the scale, speed of deployment, and completion of an RCT. Failure to complete trials designed to answer important questions must be avoided.

3. Embrace Data Flow and Interoperability Across Clinical Care and Research
A national effort, with legislation if necessary, must be in place to ensure that everyday electronic health records can interact electronically within clinical care. The national level that is embedded both culturally and electronically across environments must be sufficient to allow data to move from one clinical record to another, including the ability to receive funding from one organization and transfer of data from one organization to another, all requiring trial-specific interinstitutional agreements and contracts. This approach is in stark contrast to other industries, such as finance, which have embraced distributed data systems with cross-institutional interoperability solutions.

The NIH and the FDA are aware of the inefficiencies and have supported efforts to standardize data elements within case report forms and explore mechanisms by which adequately robust clinical data could be available directly from every electronic health record in the US. However, progress in this space has been too slow, and the research and clinical communities are paying the price. It is essential to recast RCTs as distributed data problems, with investment in common data models, distributed data analyses, and separation of clinical trial requirements from the need to use any single data-entry system.

Conclusions
Many analyses and reports will document and scrutinize what the US did well and did poorly in response to the COVID-19 pandemic. The rapid development and deployment of vaccines is surely the single greatest achievement. Despite initial concerns that the health care system would be overwhelmed, the clinical community rallied and provided care to hundreds of thousands of critically ill patients. As with the chaotic national rollout of immunizations, which shares some of the same problems, the US needs to create a more effective environment to conduct clinical research at the national level that is embedded both culturally and electronically within clinical care.

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