Opinion

Where Is America's Groundbreaking Covid-19 Research?

The U.S. could learn a lot from Britain.

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British researchers have conducted large, rapid randomized trials of dexamethasone and other drugs.Credit...Yui Mok/Press Association, via Associated Press

Using its authority to approve treatments for emergency use, the Food and Drug Administration recently allowed convalescent plasma for hospitalized Covid-19 patients. But because the large

35,000-person study on the treatment lacked true randomization and placebos, we don't really know if antibody-rich plasma actually improves mortality.

In fact, both Dr. Francis Collins, the director of the National Institutes of Health, and Dr. Anthony Fauci, the government's top infectious disease expert, raised concerns that emerging data on the treatment was not strong enough to merit emergency approval.

Convalescent plasma illustrates more than a problem with the F.D.A.'s approval process. It points to a larger shortcoming in clinical research in the United States.

Americans and American biomedical researchers have often prided themselves on conducting the best clinical research in the world. Yet with over six million coronavirus cases and 183,000 deaths, the United States has produced little pathbreaking clinical research on treatments to reduce cases, hospitalizations and deaths. Even one of the most important U.S. studies to date, which showed that the antiviral drug remdesivir could reduce the time Covid-19 patients spent in the hospital to 11 days from about 15, had too few subjects to demonstrate a statistically significant reduction in mortality.

Progress on therapeutics research has been a very different story in Britain. In mid-March researchers there began a randomized evaluation of Covid-19 therapies, known as Recovery, that involves every hospital in the nation. The goal was to conduct large, rapid and simple randomized trials to define standard treatment. Some 12,000 patients were quickly randomized — that is, assigned by chance to receive different treatments — and within 100 days of the effort's start, researchers made three major discoveries that transformed Covid-19 care worldwide.

Researchers found no benefits from the use of hydroxychloroquine in hospitalized Covid-19 patients, nor from the lopinavir-ritonavir drug combination. On the other hand, dexamethasone, an inexpensive steroid, was found to reduce mortality by up to one-third in hospitalized patients with severe respiratory complications. Each of these results was conclusive and went against the expectations of many clinicians, guideline writers and lay advocates. The results demonstrated the critical need for randomized trials to separate drugs we hope work from treatments we know work.

In the United States, by comparison, the government-sponsored Patient-Centered Outcomes Research Institute has spent millions of dollars creating a large clinical research network but has produced no research results on Covid-19 therapeutics.

That's not to say nothing has been done. In April, the institute did begin HERO, an effort to bring together health care workers to share their clinical experiences, and a randomized trial to determine whether hydroxychloroquine can prevent coronavirus infections. But so far, that trial has enrolled only 10 percent of the health care workers necessary for the trial and as a result has

reduced its enrollment targets; no useful results are likely. Only at end of July did Dr. Collins finally announce that the National Institutes of Health was preparing to begin large-scale clinical trials for Covid-19 treatments. And it wasn't until last month that the N.I.H. began two trials to test antibody treatments.

But with about 1,000 Americans and more than 5,000 others worldwide dying every day from Covid-19, taking until the end of July to begin enrolling patients in randomized trials seems a bit slow.

As the United States designs research protocols to investigate clinical therapeutics, we should ask: What has gone right in Britain that the United States can adopt to help rapidly and definitively identify Covid-19 therapeutics that really work, and just as important, those that don't?

Maybe the most important factor is an attitudinal difference: British clinical researchers have a longstanding commitment to large, simple and rapid randomized trials. American researchers prefer smaller, selective and complex trials with many restrictions on patients who can enroll.

Martin Landray, the British epidemiologist who is one of the leaders of Britain's effort, identified six other factors that contributed to its success in an interview with us. They should be applied in the United States to produce more rapid, large-scale clinical trials of Covid-19 therapeutics.

First, the Recovery trials are designed to be easy to take part in, with paperwork that is short and simple for health care providers — doctors, nurses, even medical students — to handle.

Second, the Recovery protocol was quickly approved at the national level and adopted by all hospitals in Britain.

Third, background patient data provided by the National Health Service helped to simplify the research process. Information like age, race and other health problems is already built into the hospital systems for all patients, so providers didn't have to collect it. Follow-up data is more comprehensive because post-discharge mortality can be tracked through the N.H.S. database.

Fourth, support from leaders in government health care ensured widespread cooperation by hospitals. The four chief medical officers of England, Scotland, Wales and Northern Ireland wrote to every hospital executive in their country that participating in the Recovery trial was a priority.

Fifth, Britain has a national system of research nurses who were rapidly redeployed to work on Covid-19 research at the beginning of the pandemic.

And last, the British effort was incorporated as part of everyday clinical care in hospitals. The alternative, of haphazardly trying anything and everything, which seems to have been the American way, was rejected in Britain because it neither optimizes patient care nor generates

useful data. The philosophy that clinical research is the standard of care — a philosophy common in cancer treatment — was the right and ethical approach for Covid-19.

An additional feature worth noting about the Recovery effort is that it has been relatively inexpensive to conduct. Oxford's grant for the study was roughly $2.8 million. N.H.S. clinicians recruited patients as part of their job and drugs were provided as part of the N.H.S. Even with the additional cost of paying for clinical research associates, the trial was remarkably inexpensive and has proved its value.

What Britain has done is not beyond the United States. America has health networks with comprehensive patient data on a meaningfully large scale. Though networks don't encapsulate the full population, they cover enough patients to provide background data for large clinical trials.

Moreover, the United States has no shortage of researchers, who can be deployed on Covid-19 therapeutic research, especially as many have been freed up with other research having been put on hold.

Unfortunately, unlike Britain, the United States has lacked a clear, unified message from government health care leaders, major insurance companies and hospital systems to put in place large, simple randomized trials that are considered the standard of care for Covid-19 treatment. We need to change that muddled approach now and reassert the nation's clinical research excellence.

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Correction: Sept. 1, 2020

An earlier version of this article misstated the amount of the Oxford grant for the Recovery study. It was $2.8 million, not $2.1 million.

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