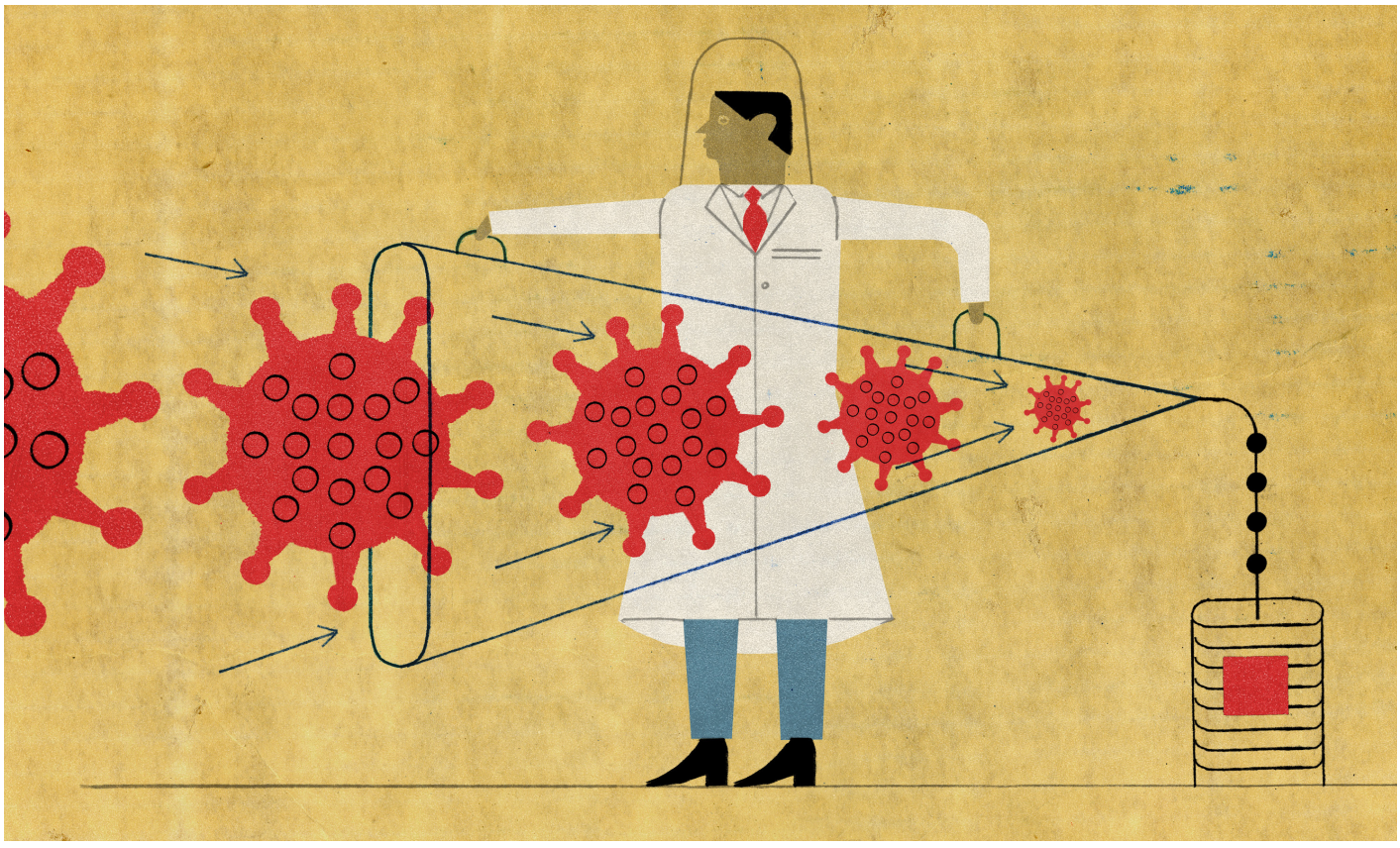

STREAMLINING the Virus Fight

A team of Oxford researchers led the world in identifying successful treatments for infected COVID-19 patients and offer a model for the future. By **BEN HIRSCHLER.**

BRITAIN HAS NOT HAD A GOOD PANDEMIC. A LATE LOCKDOWN, A lack of testing capacity and shortages of protective equipment for healthcare workers have exacerbated problems for a country with one of the world's highest coronavirus deaths rates.

Yet in one area Britain has excelled. When it comes to assessing which drugs work to treat COVID-19, a small team of scientists from the University of Oxford has led the world. Their success in proving the life-saving benefits of a cheap and widely available steroid—dexamethasone—highlights just what can be achieved by focusing on speed and simplicity.

The record pace at which the Randomized Evaluation of COVID-19 Therapy (RECOVERY) clinical trial recruited thousands of patients in hospitals the length and breadth of Britain meant researchers were able to quickly reach straightforward "yes" or "no" conclusions about the efficacy of different treatments.

RECOVERY, of course, was not the only research project launched to study the new disease. Indeed, there has been a blizzard of experiments, with more than 4,000 studies aimed at testing treatment and prevention strategies registered since the start of January, according to the TrialsTracker website. The problem is that many of these studies have duplicated efforts and the vast majority have been too small to provide definitive answers.

By contrast, the Oxford group constructed a large study with the statistical firepower to answer the urgent questions that doctors were asking—and they acted fast. "If you want to do things at scale and go fast, then you have to keep the process simple," Professor Richard Haynes, clinical trial lead for RECOVERY, said in an interview with the Brunswick Review.

ILLUSTRATION: DAVID PLUNKERT

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Early in the pandemic the Oxford researchers realized that doctors would be hunting for treatments as soon as cases started pouring into hospitals. As a result, Haynes's colleagues Peter Horby and Martin Landray wrote the protocol—or masterplan—for the trial in just two days in early March, and nine days later the team had recruited the first patient. It was unprecedentedly fast for a process that normally takes months. Within eight weeks RECOVERY had enrolled 10,000 patients.

"Speed was vital," Haynes said. "Surfing is not a bad analogy: Just before the coronavirus wave broke, we were in position, all our sites ready to go, which allowed us to recruit as many people as possible."

Grim though the situation was, the fact that Britain had a very big epidemic and a high mortality rate among hospitalized patients made it an ideal place to conduct research last spring. And by June, they had concrete results. In addition to proving that dexamethasone improved survival in patients sick enough to need breathing support, they also demonstrated that hydroxychloroquine—the malaria pill controversially endorsed by Donald Trump—and a combination of two common HIV drugs did not help.

The success with dexamethasone was the first time that a drug had been shown to help reduce the risk of death from COVID-19 in a randomized controlled trial (RCT). World Health Organization Director-General Tedros Adhanom Ghebreyesus said it gave the world "a much-needed reason to celebrate." Two former US Food and Drug Administration Commissioners, Scott Gottlieb and Mark McClellan, wrote in an editorial in The Wall Street Journal that it showed "how to learn more, faster about promising coronavirus treatments."

RCTs are the gold standard for testing medicines because they remove biases by randomising patients to received either a drug or a placebo. But they need large numbers to work and often it takes many months to recruit the thousands of patients needed, especially if studies are complicated and investigators are asked to assess multiple medical parameters.

The extraordinary circumstances of the pandemic called for extraordinary measures to streamline procedures and deliver results fast and RECOVERY proved an object lesson in how that could work. It is a notion that may well have resonance for policymakers and company executives looking back on their own handling of the crisis.

"I think what we have been able to demonstrate is that trials can be simple and simple trials can provide really important answers," said Haynes. "It may be a bit counterintuitive, but I hope we have persuaded people that actually collecting 10 times less information on 10 times more people can sometimes be hundreds of times more informative."

By keeping the trial protocol simple and not over-burdening doctors with demands for lots of data about each patient, the researchers made life easier for hospitals. That encouraged widespread participation and the trial ended up involving 176 hospital sites across Britain—essentially every acute care facility in the country. In all, it recruited more than 12,000 patients, or around one in six of all Britons admitted to hospital with COVID-19.

The centralized National Health Service certainly helped expedite the work and the National Institute for Health Research also provided vital support to facilitate a rapid nationwide takeoff. Other healthcare systems, by contrast, are far more fragmented—notably so in America. Nonetheless, Haynes and his colleagues believe that the lessons of RECOVERY could still be usefully applied in other countries if there is the right level of organization. In fact, the WHO is trying something similar at the international level with the SOLIDARITY trial, which is comparing a variety of treatment options to standard care.

As in many other fields, the story underscores the importance of learning from a crisis. In the case of medicine that means taking the opportunity to conduct scientifically rigorous experiments when offering treatments to patients that may or may not work.

But the streamlined approach to running clinical trials could also have implications for drug development outside COVID-19. Across many diseases drug trials have been getting increasingly expensive, complex and slow in recent years. The result has been a huge inflation in trial costs, with some studies now costing hundreds of millions of dollars. By contrast, the super-fast RECOVERY trial had a grant of just £2.1 million.

"There are lessons to be learned outside a pandemic situation. If you could reduce the cost of trials tenfold, then you could afford to test 10 times more drugs," said Haynes.

At its peak, the Oxford trial was recruiting 400 to 500 hospital patients every day. The rate has since fallen back to single figures, which means that enrolling enough patients to get meaningful results from the other arms of the trial will take some time. The study is also evaluating the anti-inflammatory drug tocilizumab, the antibiotic azithromycin and convalescent plasma taken from people who have had COVID-19.

The relative lull in new infections over the summer has given Britain's healthcare system time to recuperate. But Haynes and his colleagues are not resting on their laurels. Rather, they are preparing to ride any disease resurgence and to test more potential treatments, including experimental monoclonal antibodies therapies now being developed by several pharmaceutical companies.

"We haven't switched anything off. If there is a second wave, we are ready to put our foot back on the accelerator and investigate further drugs and answer more questions." ◆

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