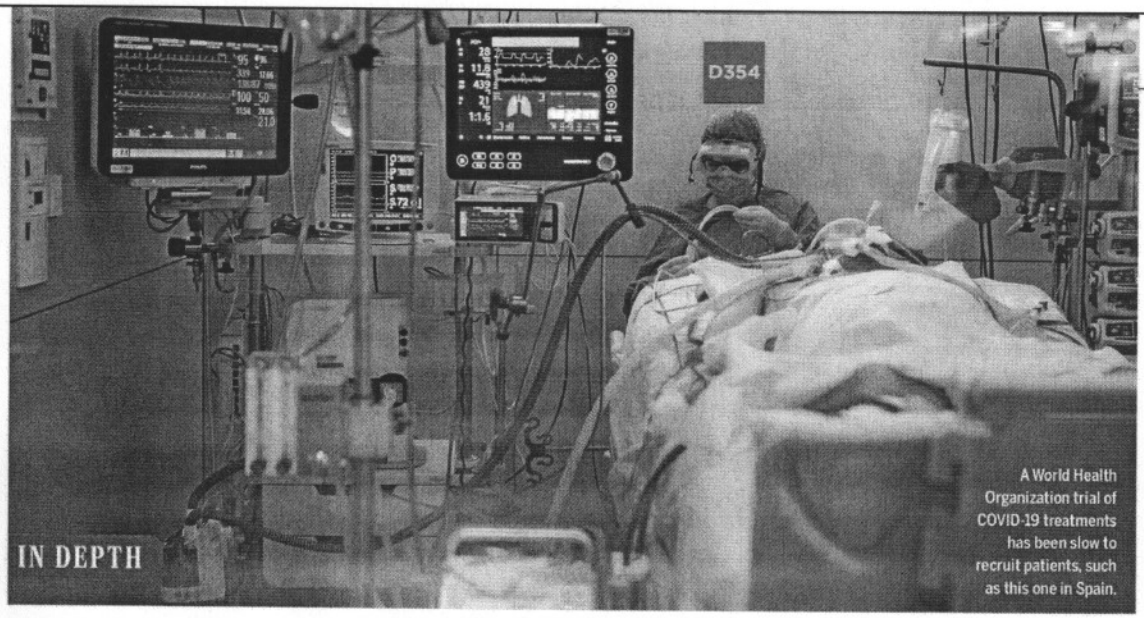

IN DEPTH

A World Health Organization trial of COVID-19 treatments has been slow to recruit patients, such as this one in Spain.

PHOTO: PAU BARRENA/AFP/GETTY IMAGES

COVID-19

U.K. megatrial outshines other drug studies

Efficient recruitment and simple design are key to Recovery trial's success

By **Kai Kupferschmidt**

On 29 June, University of Oxford clinical scientists Martin Landray and Peter Horby changed how physicians around the world consider treating COVID-19—for the third time in little more than 3 weeks. The principal investigators of a U.K. megatrial called Recovery, which has been testing existing drugs as therapies for the new disease, the pair had just finished reviewing data from 1596 patients who had received a combination of lopinavir and ritonavir, two antivirals known to curb HIV, and 3376 patients who had received only standard care. In a press release, they and their Recovery colleagues announced there had been no significant difference in the death rate between the two groups. "This could have worked. And it was a bust," says Eric Topol, director of the Scripps Research Translational Institute. "It was really important to clarify that."

Earlier in June, and again through press releases, Recovery (Randomised Evaluation of COVID-19 Therapy) delivered widely accepted verdicts on two other treatments. It revealed that dexamethasone, a cheap steroid, reduced deaths by one-third in patients on a ventilator and showed that hydroxychloroquine, the antimalarial drug controversially touted for COVID-19, did not benefit hospitalized patients. A run on dexamethasone ensued as physicians in the United Kingdom and elsewhere quickly made it part of their standard of care for the sickest patients, whereas many other studies of hydroxychloroquine now looked futile and were halted.

Large, randomized trials are the gold standard for testing a drug's efficacy. But they have been scarce so far in the COVID-19 pandemic. "Everybody has the first part about "randomized," but they omitted the "large" part, says Ana Maria Henao Restrepo, a medical officer at the World Health Organization's (WHO's) Emergencies Programme. "Every clinician, every researcher wants to help and then they end up having a trial with 300 or 400 patients that cannot come up with conclusive evidence."

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In a sea of small, single institution studies, Recovery, with 12,000 patients and hundreds of participating hospitals, stands out—and offers lessons for the few other megatrials, organized by WHO and other bodies, which have been slow off the mark. "The three Recovery trials are the best trials that have been performed to date," Topol says.

One reason Recovery has done so well is that it is backed by the United Kingdom's centralized National Health Service (NHS), involving 176 of its hospitals. In the United States, where the health care system is fragmented, the National Institutes of Health has only begun a few large trials so far and completed just one, a study of Gilead Sciences's antiviral compound remdesivir that showed COVID-19 patients given the drug recovered faster. The dearth of results from a country that has seen more cases of COVID-19 than any other is "surprising and a bit disappointing," says John-Arne Røttingen, who heads the steering committee of Solidarity, WHO's attempt to evaluate repurposed drugs as possible COVID-19 therapies.

In contrast, Recovery took advantage of the United Kingdom's own bungled public health response to the new virus, which has led to Europe's largest outbreak and the third most deaths in the world so far. "They have been able to recruit well, because they have had a lot of hospitalized patients," Røttingen says.

In a letter to all NHS hospitals, the United Kingdom's five most senior doctors urged health care workers to enroll patients in Recovery and two other important trials. "Use of treatments outside of a trial, where participation was possible, is a wasted opportunity to create information that will benefit others," the doctors, including Chris Whitty, chief medical officer for England, wrote. Because of that coordination, "One in every six COVID-19 patients that come into the U.K. hospitals go into the trial," Landray says.

Organizers also kept Recovery simple, allowing any NHS hospital to participate. Inspired by trials of heart-attack treatments that his Oxford colleague Richard Peto and others did in the 1980s, Landray says they radically cut down on the data health care workers need to collect, with only a few questions asked at enrollment and at just one later point: when the patient dies, is discharged, or 28 days after enrollment. Clinical trials have become excessively cumbersome in recent years, Landray argues.

Solidarity has a similarly straightforward design, but its more international nature has proved a challenge. The trial, designed to test four treatments—hydroxychloroquine, lopinavir/ritonavir, interferon beta plus lopinavir/ritonavir, and remdesivir—was announced on 20 March and enrolled its first patient in Norway 1 week later. But rolling out the trial in dozens of countries has meant getting approval from dozens of regulatory agencies and ethics boards as well. "That has taken a surprisingly long time in many jurisdictions, including in Europe," Røttingen says, and recruitment in Europe slowed over time as the epidemic subsided. "When countries were ready to sort of start, the epidemic was under control in many ways," he notes.

"The three Recovery trials are the best trials that have been performed to date."

Eric Topol, Scripps Research Translational Institute

A European trial called Discovery, coordinated by the French research institute INSERM and meant to join with Solidarity in testing the same drugs, also fell short. The goal was to enroll 3200 patients across the continent. The study almost met its goal of 800 participants in France, but it barely managed to recruit patients elsewhere. Although France funded its part of the trial, it expected partner countries to pick up their own tabs. "One of the issues was that not all the countries had funding," says Yazdan Yazdanpanah, head of infectious diseases at INSERM.

Meanwhile dozens of small trials competed for patients in countries, most of them focusing on the same drugs, such as hydroxychloroquine. "I don't understand why everyone was looking at the same thing," Yazdanpanah says. "I think we can do better." Susanne Herold, an expert on pulmonary infections at the University of Giessen, agrees. "There needs to be more coordination both within countries and across borders," she says.

Another problem has been the widespread use of treatments outside of randomized trials. Landray notes that tens of thousands of COVID-19 patients in the United States have been given convalescent plasma, for instance, but not alongside a group receiving a placebo. "We'll know what happened to those patients, but we won't know whether they would have been better off actually, if they hadn't got the convalescent plasma." Convincing clinicians that therapies still need to be tested can be difficult, Henao Restrepo says. "Some are convinced they know which drugs work."

She still has high expectations for the Solidarity trial. "The preparatory work is paying off," she says. Its recruitment has picked up as more countries, many with surging cases such as Iran, have joined. So far, 39 countries are participating and 60 more signing up. "One of the advantages of such a global trial is that you can follow the pandemic as it evolves," Røttingen says.

With recruitment running at about 500 patients per week now, Solidarity's two remaining treatment arms—it stopped the hydroxychloroquine and the lopinavir/ritonavir ones as results emerged—are likely to yield answers soon, raising the question of what drugs to test afterward. More repurposed drugs are being discussed, but increasingly the attention is turning to monoclonal antibodies targeting the virus.

Henao Restrepo thinks the international nature of Solidarity makes its results more generalizable and likely to be accepted. Herold expects that the Discovery trial contribute as well. Started in part to supplement Solidarity, it collects not only basic mortality data, but also information on viral levels and blood parameters. Those data can indicate not just which drugs are effective, but also how they work and at what stage of the disease.

The Recovery trial continues, with its team scrambling to publish full results. Some researchers have criticized its practice of releasing important results as press releases; so far, it has given details for only one of the three headline findings, on dexamethasone, in a preprint posted 6 days after the release. The Recovery team is still collecting trial data on the antibiotic azithromycin, an antibody called tocilizumab, and the antibody-rich plasma collected from recovered patients.

Results on those therapies are likely months away, Landray says. But he cautions he has been wrong before. On the morning of 4 June, he had predicted the first results from Recovery would likely come in early July. A few hours later, the chairperson of the trial's data monitoring committee called him to say there was enough patient data to declare a verdict on hydroxychloroquine. ■

COVID-19

Can interferons stop COVID-19 before it takes hold?

Biology of infection supports early treatment with body's own viral defenses

By **Meredith Wadman**

On 30 April, Valerie McCarthy's test result confirmed that her grinding fatigue and pummeling headaches were caused by the new coronavirus. She wasn't hospitalized, but the very next day, a nurse at Stanford University Medical Center gave the 52-year-old marathon runner an injection that contained either a placebo or a natural virus fighter: interferon.

McCarthy was Patient 16 in a clinical trial that, it's hoped, will help fill a huge void in treatments for COVID-19: Doctors have no drugs that, given early, have been proven to prevent infection or help beat back the virus before it takes hold. So far, the two scientifically validated treatments for COVID-19—remdesivir and dexamethasone—have only been shown to work in hospitalized patients with serious illness.

But a small flurry of recent papers suggests the novel coronavirus does some of its deadly work by disabling interferons, powerful proteins that are the body's own frontline defenders against viral invasion. If so, synthetic interferons given before or soon after infection may tame the virus before it causes serious disease—a welcome possibility that additional recent studies support.

Several interferons were approved decades ago by the U.S. Food and Drug Administration, their immune-boosting powers deployed against diseases including cancer and hepatitis. And in an early, unrandomized preventive trial in a hospital in China's Hubei province, none of 2415 medical workers who took daily interferon nose drops got the virus, according to a medRxiv preprint.

The Stanford trial is one of dozens now trying interferons against COVID-19, including in people who aren't sick but might have been exposed to the virus. First results from a controlled trial at the Univer-