



Newcastle upon Tyne

stokel@gmail.com

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## CORONAVIRUS PANDEMIC

# On the road to Recovery—the world's biggest covid-19 treatment trial

When it comes to covid-19 therapeutics, the UK is the world leader, spearheaded by the largest, most successful trial in the world. **Chris Stokel-Walker** looks at Recovery, and why it has proved hard to replicate elsewhere

Chris Stokel-Walker *freelance journalist*

It's hard to overestimate the impact of the Recovery trial. In just one year, it's thought to have saved up to a million lives worldwide. Its finding that the low cost steroid dexamethasone reduces death from covid-19 by up to one third is arguably the major drug discovery in covid treatments so far.<sup>1</sup>

Hatched on a London bus ride on 9 March 2020,<sup>2</sup> Recovery quickly became—and remains—the largest covid-19 treatment trial in the world, with nearly 40 000 patients enrolled at 181 sites globally, helping to shape the treatment of patients worldwide during a live and ever-changing pandemic.

"We realised—on the now famous bus trip—that we had to get a treatment trial up and running into routine clinical pathways within hospitals in advance of the pandemic really hitting hard," says Martin Landray, deputy chief investigator of Recovery. "We were fighting a deluge of admissions to hospital," says Ian Hall, director of the Nottingham Biomedical Research Centre and a principal investigator in Recovery, of the early days of the pandemic. "Everybody was under enormous pressure back then," says Landray. "You've got to do something. We can't wait another two months to get a result. People are dying today."

### We love the NIHR

The UK has historically made significant investments in infrastructure—largely through England's National Institute for Health Research (NIHR)—that enable it "rapidly to roll out clinical studies across multiple centres if there's a need to do so," says Hall.

"We really have got it right here in the UK," says Emmanuelle Denis of Oxford University, who is supporting Recovery as it expands internationally. "And, partly, it's the integration of the NIHR with the NHS."

Both the NIHR and UK Research and Innovation, which acts as a non-departmental government funding body, provided significant funding for coronavirus trials, as have independent non-profit organisations like the Wellcome Trust, which co-funds Recovery.

At the same time, the Medicines and Healthcare Products Regulatory Authority (MHRA), which regulates clinical trials, cut the amount of time to approve covid-19 studies 10 fold, down from around 60-90 days to just 6-10 days.

The MHRA's streamlined approach enabled Recovery to enter the field within nine days. This required a rethink away from the overly cautious, risk averse approach that has pervaded medicine, says Landray.

"Very often trials are seen as being risky, and not to do trials is fine as a sort of unjustified faith in the quality of the evidence base that goes behind routine care," he told *The BMJ*. Yet, in reality, much of medicine isn't based on evidence from formal clinical trials but on physicians' intuition, supported by prior cases. Landray points to cardiology, where he estimates just 15% of clinical guidelines are based on robust evidence from randomised trials—"and cardiology is probably at the top of the evidence based tree," he says.

Every hospital across the country was set the challenge of enrolling one in 10 of its covid-19 patients into the trial, a target it succeeded in achieving. Some hospitals, led by individual doctors, managed to recruit at an astonishing rate.

It also eliminated some of the political egos that can clog up clinical trial approval, Hall adds. "Many clinical academics or centres feel somewhat competitive about the way they work and think they know how to do it—and that their colleagues down the road don't do it as well. But any differences that might have existed were largely put to one side."

### Red tape cut

Landray says, "The really important thing was stripping away everything else that doesn't matter." For example, a recent analysis of four covid-19 vaccine trials' consent documents found that their average length was 8333 words, requiring participants to read for 35 minutes to provide consent.<sup>3</sup>

Among the most lauded features of Recovery is its clear endpoint: does the drug reduce mortality? "If one in four people who go into hospital are dying, then the thing we need to know is: 'Does drug X reduce the risk of dying?' And if it does, will almost everything else be by the by?" says Landray. We already know, for instance, that steroids increase blood glucose, and the risk of infection, "We didn't need to know that all over again by running it in the trial." Likewise, the use of pre-existing primary care data enabled duplication of work already done. "Don't ask someone who is desperately breathless, 'What's your ethnic background?'" Landray says.

With Recovery, he says they practically started with a blank piece of paper and built the trial from the

bottom up rather than adapting from previous documentation as often happens in trials. It's something Landray would like to see repeated, certainly in any future pandemic. "I've been in so many meetings where people have talked about how what we need is coordinated and internationally harmonised rules," he says. "We don't need harmonised; we want simplified."

Nathalie Strub-Wourgaft, director of covid-19 response for the Drugs for Neglected Diseases Initiative, agrees. "We've had too much fragmentation and duplication of clinical trials," she says. "We've had such a big disparity worldwide between different trials, that this idea of harmonising trials across countries seems sensible, and reducing duplication is good."

## Going global

Over a year since Recovery first started, the UK remains the leader in covid-19 treatment trials, running more than anywhere else. That seems remarkable given the pandemic's continuing grip around the world.

Even the US, with the world's biggest economy and the heaviest covid-19 toll, has just one major therapeutics trial—Activ-3 run by the National Institutes of Health and with 10 000 participants. "I don't think that's down to a lack of will within the US," says Hall, "it just seems to be more difficult. They haven't—I don't think—invested in the underpinning infrastructure in quite the same way."

The second largest covid-19 therapeutics trial—the World Health Organization's Solidarity—reported interim results for four drug treatments from 405 hospitals in more than 30 countries in October 2020, just six months after launching.<sup>4</sup> None of the four showed an improvement in patient outcomes. After a seven month pause, on 7 May, WHO announced a second phase focused on inflammation.<sup>5</sup> Why it took over half a year to start the next phase is uncertain: WHO did not respond to requests to comment for this story. Sources *The BMJ* spoke to were cagey about commenting on the delay, but attributed it to high levels of bureaucracy and the challenges of coordinating many different countries.

Strub-Wourgaft helps oversee the Anticov trial, conducted across 13 African countries by 26 partners. "You duplicate the questions by 13 when you have 13 countries," Strub-Wourgaft says. All the problems that Recovery could quickly expedite—including political sensitivities—become more difficult when dealing with so many countries who want to manage things according to their own culture, she says.

When she proposed the terms of the Anticov trial to the countries participating, she received more than 300 questions. Some were duplicated across countries, but many weren't. "They have to do it right, and to do it right, they need to take time," Strub-Wourgaft says.

Anticov only got going in November 2020, recruiting participants to test a drug combination of nitazoxanide and ciclesonide to treat mild and moderate cases of covid-19.

Strub-Wourgaft freely admits to being jealous of Recovery's fast track processes, prioritisation, and resources. "The problem in low and middle income countries is that you don't have all those resources that are up and ready to be mobilised."

In February, Recovery launched an international expansion to its trial,<sup>6</sup> starting in Indonesia, Nepal, and Vietnam (Denis, who is liaising between them and the UK team, told *The BMJ* that there are also plans to launch an arm in Ghana). At the time of writing, there are 127 participants across four sites.

Recovery International aims to find alternative treatments and therapeutics that can be used in areas where medical and infrastructural resources are weaker than in the UK. It initially planned to test the efficacy of aspirin and colchicine against covid-19 but has now switched to more promising therapeutics: a high dose dexamethasone course of treatment, and the monoclonal antibody infliximab.

The teams took pains to reset expectations of speed from the off. "In the UK, the trial could be rolled out rapidly thanks to the joined-up nature of the NHS," reminds Denis. "Where Recovery in the UK was able to streamline a lot, we're finding that it may be more difficult to do that in other places."

One way they hope to speed up approval is with the support of the MHRA, that has offered to talk to other countries' regulatory authorities to "reassure them and share their experiences," says Denis.

"I can't tell you how exciting it is to be part of Recovery," she says. "It's going to be a game changer for academic led clinical research. It will show that you can strip away a lot of the extras that are expected to be done and take a really risk based approach."

"When you look at it and see how many people have been helped, just by dexamethasone, it will help to persuade regulators in the long run of the benefits of taking a more pragmatic, streamlined approach in trials like this where you're using known drugs."

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