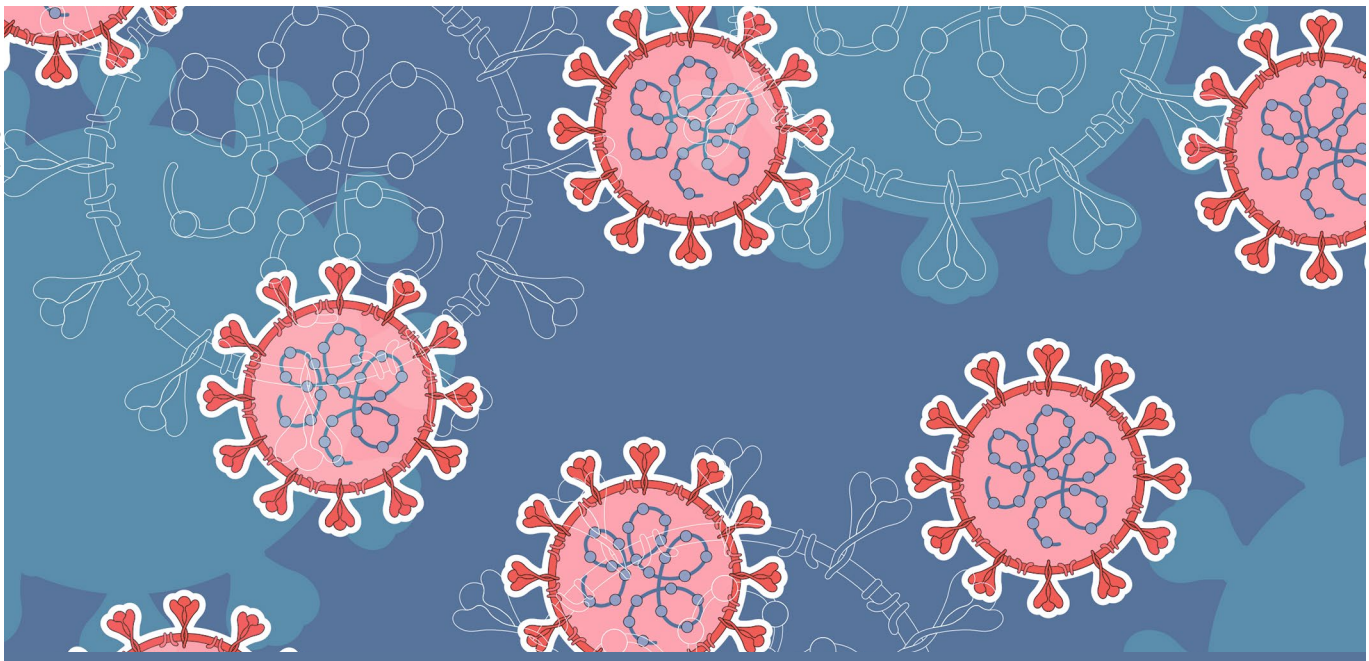

Long COVID's long R&D agenda

As researchers work to understand the biology and epidemiology of post-acute COVID-19, a pioneering platform trial is now testing treatments to try to address the long-term complications of infection in previously hospitalized individuals.

Asher Mullard

In late April, the HEAL-COVID trial will start recruiting COVID-19 survivors from hospitals in the UK to study treatments that could reduce the long-term effects of SARS-CoV-2 infection. For Charlotte Summers, lead investigator of the trial and an intensive care specialist at the University of Cambridge, the trial couldn't come soon enough. "Hospitalized patients who have survived hospital discharge think 'woohoo, I'm through the worst of it'. But actually, that's not the end of the story by a long shot," she says.

Certainly, hospitalized COVID-19 patients have been particularly hard hit by the long-term effects of infection. Roughly 12% of these patients die within months of being discharged from the hospital, found a recent analysis of nearly 48,000 patients in the UK. Nearly 30% are re-admitted to hospital. Respiratory disease, cardiovascular disease and diabetes diagnoses are also raised in these individuals compared with matched controls.

The long-term impacts of infection on non-hospitalized COVID-19 patients are more difficult to assess, but a concerning picture has emerged there as well. The World Health Organization (WHO) estimates that 10% of COVID-19 survivors — including both hospitalized and non-hospitalized individuals — have persistent problems 12 weeks after infection.

Long COVID manifests in various ways, affecting the heart, the lungs, the gastrointestinal system, the brain, mental health and more. The most common reported issues are breathlessness, fatigue, smell and taste disturbance, and anxiety, found a living systematic review of studies of the condition in hospitalized and non-hospitalized patients. For some individuals, these issues can be debilitating.

But as yet there is still limited insight into the true scope and scale of this post-viral problem. The underlying biology, too, is unclear.

Following a series of workshops by the NIH, the ISARIC and GloPID-R and the WHO, a research agenda for long COVID has now emerged. The WHO is working to harmonize global research efforts. The NIH is investing US$1.15 billion over the next 4 years to better understand the long-term effects of COVID-19, with an eye to both prevention and treatment. And the first-of-its-kind HEAL-COVID platform trial provides one template for what future trials in this space could look like.

"I think long COVID is getting the attention it deserves," says Peter Horby, Professor of Emerging Infectious Diseases and Global Health at the University of Oxford and co-lead on the UK's RECOVERY platform trial for acute COVID-19. "But it's a challenging area."

The R&D agenda

The difficulties of studying long COVID — a term first coined by a patient on Twitter — start with definitions.

"Long COVID doesn't really have a meaning: it's used to cover a whole soup of stuff," says Summers. All sorts of individuals have adopted this term, from patients who were hospitalized owing to severe COVID-19 to those who had milder or even asymptomatic infections, with or without a positive

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SARS-CoV-2 test. The symptoms reported, meanwhile, affect nearly every organ system.

'Post-acute' COVID-19 — the umbrella term embraced by the NIH to capture prolonged health abnormalities in people who have been infected with SARS-CoV-2 — covers a broad space as well. It includes not just long COVID, but also the effects of potentially overlapping sequelae like post-intensive care syndrome (PICS), a condition associated with treatment in an intensive care unit.

For Janet Diaz, lead of COVID-19 clinical management response at the WHO, clearer definitions and accepted terminology are key to ensuring that researchers around the world are working on the same problems. To this end, the WHO is surveying clinicians and patients to narrow in on a consensus definition of a "post-COVID" condition. "We hope to have some sort of definition ready in May that could be valid at least for the next 6 months until we know more," says Diaz.

In February, the WHO also released a case report form to harmonize data collection. The 11-page document includes hundreds of questions, covering pre-existing conditions, the course of the acute COVID-19 illness, vaccination status, the incidence of symptoms after acute COVID-19 illness and more. Consistency is critical for the comparability of long COVID study results, says Diaz. The WHO is working on releasing a streamlined core form as well.

There is also an urgent need for better quality data on the epidemiology of post-acute conditions. "The data are still fragmented, but I do think that there are efforts to coordinate and integrate them," says Diaz.

Many of the earliest insights into long COVID were collected via online surveys, organized by patient advocacy groups. A small but growing set of studies have captured more data on the scope of the problem, but these analyses are still mostly based on small numbers of affected individuals. Larger, prospectively designed, observational studies — such as PHOSP-COVID, in 10,000 hospitalized patients, and LIINC, in 800 individuals with SARS-CoV-2 RNA positivity — are capturing longitudinal data from COVID-19 survivors. But a shortage of comparisons with matched control groups could yet be problematic.

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"It's important not just to look at the symptoms in isolation, but actually to look at what are they over and above what one would expect for a patient of a given description," cautions Shamil Haroon, a primary care specialist at the University of Birmingham and the co-lead investigator for the observational TLC study of long COVID in the UK. "Much of the literature does not have a control population, which is a real limitation. It makes it almost impossible to make any inferences about how the virus impacts an individual."

The TLC study represents an effort to fill this knowledge gap. The study will enrol at least 2,000 non-hospitalized patients who have had long COVID symptoms for at least 12 weeks and a positive SARS-CoV-2 test. It will also enrol at least 500 matched controls who have not had a positive SARS-CoV-2 test or suspected COVID-19.

"What we need to do is compare long COVID patients to others who are similar in every other respect, other than that they haven't had COVID-19," says Haroon. After all, the pandemic might have impacted health outcomes across the board, regardless of infection status. Increased stress and anxiety levels, reduced access to care for individuals with underlying health conditions, and other factors could all have taken a toll.

TLC study participants will use a digital platform — the Atom5 mobile phone app — to provide comprehensive self-reported details of their long COVID symptoms and quality of life. A subset of around 300 participants will also provide blood samples and biological data for researchers to assess.

Other cohort studies with non-infected control groups are also ongoing elsewhere, including in the USA and in Canada.

Data from these studies will be key to subcategorizing long COVID patients into different populations, notes Haroon. "We know that patients report a very wide range of symptoms, but do those symptoms actually cluster together in ways that are due to different underlying, common disease pathways?" he asks. Such insights will be vital for identifying the right patient population to enrol into any eventual clinical trials of a given intervention, he adds.

The first funding opportunities for the NIH's expansive Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) initiative are similarly aimed at addressing epidemiological issues. A call for 'SARS-CoV-2 recovery cohort studies', for example, will support rigorous and robust characterization of the prevalence, natural history and clinical spectrum of COVID-19, again with comparisons to appropriate control groups.

> Without knowing the pathophysiology, it is a little bit of a challenge to design trials

This is the right way forward, adds Horby. "Long COVID is likely a mixture of different things, in different people, for different reasons. You do need quite intensive cohort studies to tease these factors apart."

Mechanisms make the medicine

There is also an urgent need to understand the biological mechanisms underlying the different post-acute COVID-19 symptoms. "Without knowing the pathophysiology, it is a little bit of a challenge to design trials," says Diaz.

Numerous possibilities have been proposed.

During the acute phase of COVID-19, direct viral toxicity, immune system dysregulation and more can wreak havoc on different organs. Lingering cellular damage or subsequent scarring might cause some of the longer-term problems. The immune system might remain out of whack even after the infection has resolved, with autoantibodies and other immune responses driving deleterious effects. Or, a lasting viral reservoir and residual viral material might be the issue.

"I always like to leave an 'and', because there could be other mechanisms that we haven't hypothesized yet," adds Andrea Lerner, a medical officer at the NIH's National Institute of Allergy and Infectious Diseases. Multiple mechanisms may also be in play at the same time, she adds.

Biomarker data from the cohort studies could provide some insights into the underlying biology of long COVID. The NIH is also funding autopsy cohort studies, with a focus on the histopathology of the brain and other organs and tissues, to identify the types of damage that track with different disease symptoms.

New and improved animal and in vitro models of SARS-CoV-2 infection are also in development, and these could shed further light on the biology of long COVID.

Trialling times

Despite the many open questions, a few researchers are already starting to test whether some drugs might be able to

reduce the long-term effects of COVID. The HEAL-COVID trial, for example, is hoping to show benefit in a particularly hard-hit population. "You've got to make a big problem tractable, so we will try and move the needle on readmission and death," says Summers.

HEAL-COVID will initially recruit and randomize 2,000 hospitalized COVID-19 survivors who are on track to be discharged. These volunteers will receive standard of care or one of three treatments. Apixaban, a factor Xa-inhibiting anticoagulant, is being tested based on the possibility that increased incidence of thromboembolic events could be the cause of death, breathlessness, cognitive fogginess and more. Patients in the apixaban arm will take the drug twice daily for 14 days. Atorvastatin, a lipid-lowering HMG-CoA reductase inhibitor with pleiotropic effects, might provide benefit by acting as an anti-thrombotic, an anti-inflammatory and by improving endothelial function. Patients in the atorvastatin arm will take the drug twice daily for 12 months. A third candidate has not yet been selected.

Following the model of the RECOVERY trial — a platform trial that has now tested 13 drug candidates in nearly 40,000 hospitalized COVID-19 patients — HEAL-COVID will keep adding more patients and treatment arms as needed. As such, the investigators hope to avoid the pitfalls of the underpowered and insufficiently informative studies that have dominated the COVID-19 trial landscape.

While the primary end point is hospital-free survival at 12 months, interim analyses at 90 days could help to provide earlier glimpses of activity, or lack thereof. Secondary end points will look at other measures, including fatigue, breathlessness, anxiety and quality of life.

HEAL-COVID faces numerous challenges, including the need to demonstrate treatment benefit in individuals who may be suffering from overlapping syndromes. Some of the patients enrolled into the trial will be at risk for PICS, a catch-all term for the lasting physical, cognitive and psychological impairments that affect critically ill patients after treatment in an intensive care unit.

Summers takes a pragmatic view. "Will we be able to pick out what is due to PICS and what is due to post-COVID? No, probably not. Does it matter if the therapies make them better? Probably not," she says.

> You've got to make a big problem tractable, so we will try and move the needle on readmission and death

There are also more practical considerations. "This is a very different space than acute COVID-19, because we haven't got access to all the backup and infrastructure and resources that you would normally have in hospital. We're recruiting people that have been to the hospital and we're not going to see them again," says Summers. Again following the RECOVERY model, HEAL-COVID will instead leverage linked-up electronic health-care records to collect its data.

"It's a good study, and I'm glad it's being done," says Horby, who is not involved in the trial. "I just wish it could have been started earlier."

Platform trials in acute COVID-19 — such as RECOVERY, the WHO's Solidarity trial, REMAP-CAP and the NIH's ACTIV trials — might also provide insight into long COVID treatment options, adds Diaz. If short-term use of a drug during the acute phase of COVID-19 reduces the long-term effects of infection, secondary end points from these trials might pick up efficacy signals, she explains.

"The follow-up studies of patients that have been enrolled into these clinical trials are an important opportunity," says Diaz. But insights from many of these trials may be limited to improvements on high-level clinical outcomes such as death, re-hospitalization and subsequent disease diagnoses, rather than for efficacy on subtler biomarkers or in patient-reported quality of life measures.

A longer wait

Researchers are also gearing up to tackle long COVID in patients who overcame their SARS-CoV-2 infections in the community, rather than in hospitals.

The NIH's soon-to-start ACTIV-6 trial, for example, will test up to 7 repurposed drugs in 13,500 non-hospitalized patients with mild-to-moderate COVID-19. Although the trial is primarily aimed at reducing the duration and severity of the acute infection, it will also assess impacts on long-COVID symptoms at 90 days.

ACTIV-6 investigators have not yet disclosed what drugs they will test.

Researchers are also laying groundwork in other ways.

The same tools that the TLC study will use to collect data on long COVID symptoms and quality of life might be viable as patient-reported outcome end points for follow-on trials, for example. The TLC study also includes a pilot phase, during which it will test the feasibility of delivering a rehabilitation-based intervention to patients via its digital platform. "We want to use the same platform to then trial drugs," says Haroon.

> We need to be ready so that the very moment people hit the front doors of hospitals or health-care settings, everything's ready to go

Already, he is on the look out for possible interventions, pharmaceutical and otherwise. Haroon and colleagues are reviewing the literature and classifying these into three categories: interventions that are already supported by enough evidence to be suggested to patients; those with genuine equipoise, which need to be trialled; and those that are unlikely to work or that could be harmful.

"In terms of drug therapies, a lot of that will go in the second category," says Haroon. Rehabilitation-based non-pharmacological interventions may offer faster recourse for some patients, though.

Post-viral preparation

The results from many of these efforts may come too late for the tens of millions of individuals who are already grappling with long COVID. But case counts are also still rising. "People are going to continue to have post-infectious sequelae, and we hope to help as many of them as we can," says Lerner.

With a research agenda in place, moreover, patients infected with other viruses may stand to benefit. The coronaviruses that caused MERS and SARS, as well as the influenza virus and other viral pathogens, have all been implicated with longer-term sequelae. "A post-viral syndrome phenomenon, anecdotally, is well recognized. There just hasn't been much of a spotlight on it," says Haroon. The CDC lists viral infections as a hypothesized cause of myalgic encephalomyelitis/chronic fatigue syndrome, which shares some characteristics with long COVID.

As investigators gain insight into appropriate control groups, background symptom rates, clinical trial designs and the biology of long COVID, they may be able to make inroads against other post-viral syndromes.

Progress with long COVID will also leave the community better positioned to act the next time a pandemic strikes.

"We need to be ready so that the very moment people hit the front doors of hospitals or health-care settings, everything's ready to go," says Summers.