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The medical WHAT-IF that could change clinical trials forever

The 2009 emergence of H1N1 led a few medical professionals to realise how unprepared they were. An informal group including an ICU doctor, care clinicians and a statistician met irregularly for more than a decade to create a thought experiment – a groundbreaking system that could quickly gather and analyse data and offer treatment suggestions for an unknown pandemic pathogen. As **TANIA EWING** reports, their timing was impeccable.

Before 2009, the town of La Gloria, about 200 kilometres east of Mexico City in Veracruz province, Mexico, was little known and generally unremarkable. Perched amid mountain peaks at 2460 metres elevation, the town of about 2200 residents is a major pig-farming centre: the Granjas Carroll de Mexico farm about 8km from La Gloria raised nearly 1 million pigs in 2008.

In 2009 a new strain of the H1N1 influenza emerged. Within weeks, swine flu (as it became known) was spread by international travellers, eventually affecting 74 countries and, according to the World Health Organization, killing as many as 575,000 people. Swine flu's zoonotic origins have never been confirmed, but La Gloria was in the frame early as a likely starting place because one of the earliest cases – in a five-year-old boy named Édgar Hernández – was traced there. (Much later, in 2016, a research team from the Mount Sinai School of Medicine, US, declared that the virus likely came from pigs in a very small region of central Mexico, but didn't name La Gloria.)

Professor Steve Webb, an intensive care doctor at Royal Perth Hospital, remembers the winter of 2009 as one where "we were flooded with swine flu". In the hospital's 24-bed intensive care units (ICUs), up to half the beds were filled with people infected with H1N1 and on ventilators.

"I remember thinking 'We need to be better prepared for this sort of thing'," Webb says. He and a group of international colleagues wrote a paper that was published in the *New England Journal of Medicine* (NEJM) on the swine flu pandemic. While the paper largely described the cases, the severity of the disease and its impact on ICUs, "it didn't – and couldn't – detail what treatments had worked for which patients. In ICU we just threw whatever we could at patients to keep them alive."

Webb started wondering about ways in which the next pandemic could provide better and timely information to clinicians about which treatments worked, and which did not. By definition, a pandemic has thousands, if not hundreds of thousands, of cases – so getting the numbers wouldn't be a problem. How could they collect and use that data better?

Mural by urban artist Applez, in Mexico City.

PEDRO PARDO / GETTY IMAGES

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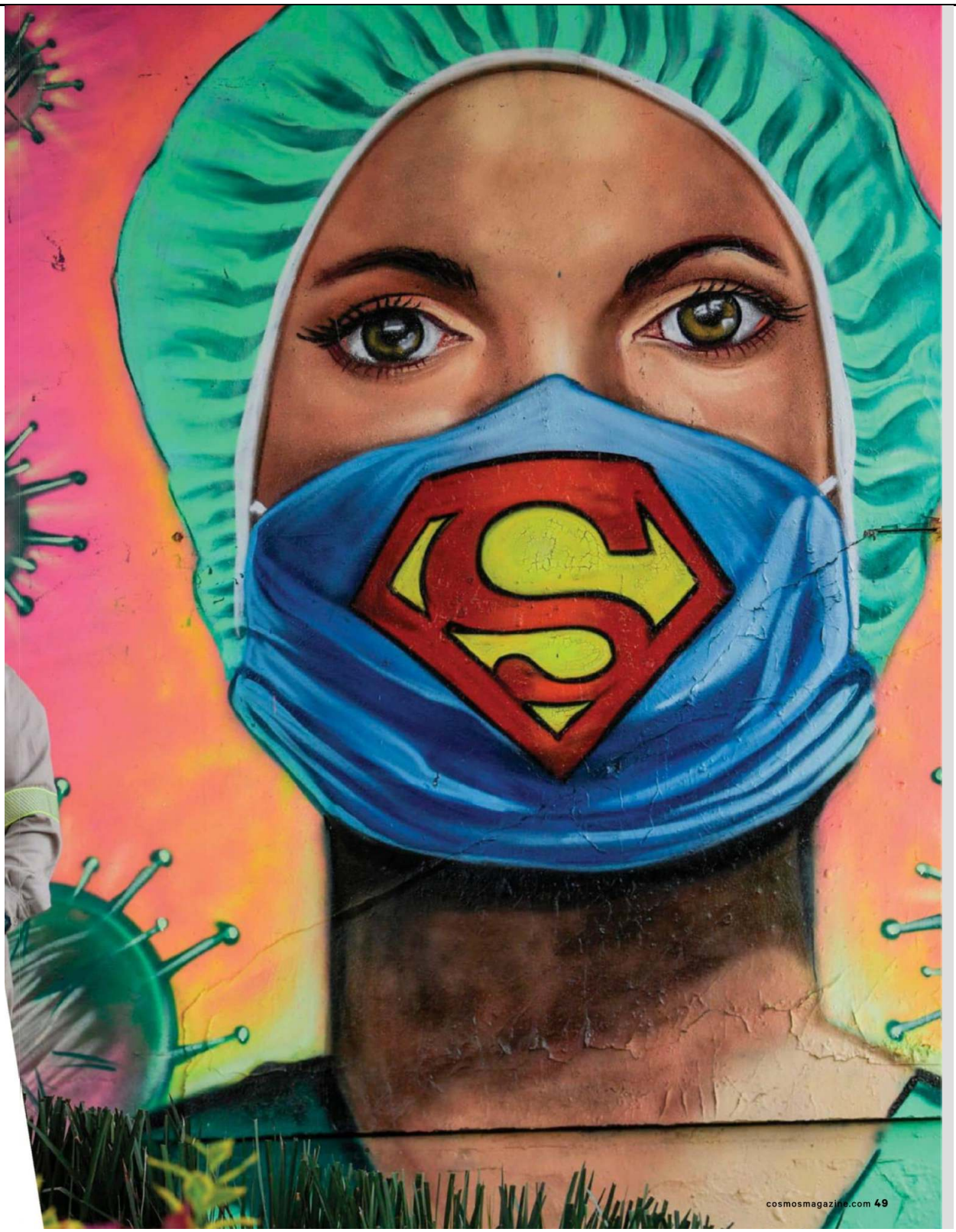


Unknown artist's work in Pontefract, northern England.

Webb – then and now also Professor of Critical Care Research at Monash University in Melbourne – and a group of intensive care clinician researchers including Derek Angus, Chair of Critical Care at the University of Pittsburgh Medical Center, and Roger Lewis, an emergency doctor and statistician in Los Angeles, started to meet around once a year to work out what could be learnt from what went wrong in 2009. They all had big day jobs; the pandemic thinking was just a side hustle. They'd squeeze their catchups onto the back of international meetings, connected by a certainty there would be another pandemic that would likely be a respiratory disease, and a drive to minimise a new infection's potential devastation.

The only unknowable was when the next pandemic would arrive.

Steve Webb
Professor of Critical Care Research, Monash University

Standard clinical trials are "equivalent to building an arena for a football game and then knocking it down and rebuilding it again for the next game. In a pandemic we knew we wouldn't have that luxury of time"

Flipping the clinical trial paradigm

The WHO has identified influenza pandemics as one of the top 10 threats to global health. In an influenza pandemic, such as swine flu, most people are admitted to ICUs with what is called Community-Acquired Pneumonia (CAP). CAP is the most common form of pneumonia; its causes are bacteria or bacteria-like organisms, fungi or viruses, such as swine flu.

In the years following the swine flu pandemic, Webb and his colleagues focused on developing a new type of clinical trial. Standard clinical trials are laborious in their genesis, often taking up to a year to begin: funding and ethics approval must be obtained and protocols developed before patients are even recruited.

"What we needed was a clinical trial that could be up and running within a couple of weeks after a pandemic hit," Webb says.

But how could they streamline the clunky, bureaucracy-laden, decades-old clinical trial process into one that could adapt to whatever a pandemic would bring, while retaining statistical rigour and patient safety?

In 2010, father-and-son team Drs Don and Scott Berry – experts in clinical trial statistics based in Texas – had designed the I-SPY2 trial, aimed at testing new drugs in high-risk breast cancer patients. It was a novel approach to bring multiple interventions into a large single trial. Its secret lay in Bayesian statistics, which involves the continual reassessment of competing hypotheses in the presence of new evidence. In essence, Bayesian statistics allows the trial design to shift and adapt as knowledge is gained. According to Scott Berry, traditional clinical trials are based around "one question and once that question is answered, then the whole trial is dismantled. And the whole process is rebuilt from scratch to answer the next question," he says, speaking from his home in Austin, the Texas state capital.

"It's equivalent to building an arena for a football game and then knocking it down and rebuilding it again for the next game. In a pandemic we knew we wouldn't have that luxury of time."

To the Berrys, broadening the scope of their Bayesian-based platform trial to a global pandemic made sense. By the time the Berrys joined Webb and colleagues in 2010, the still small group had swelled with members from Europe, Australia, the US, New Zealand and Canada. They continued to convene when they could, still sneaking in meetings after symposiums and sessions at critical care meetings and conferences they were already slotted, and funded, to attend.

The group's emphasis was on developing a platform trial and a network of ICUs that was like the I-SPY2 trial, but with global reach and system-ready when a pandemic hit. A global ambition, but for the clinicians and statisticians who were working on it together, it remained a side hustle.

OLI SCARFF / GETTY IMAGES

TRADITIONAL CLINICAL TRIAL

A traditional clinical trial is a very expensive and time-consuming process, taking many years and substantial resources to progress from phase I to IV. Many trials won't go the distance – they'll be terminated at the end of a phase.

In each trial phase, participants are randomised in equal proportion to different treatments and the trial finishes when a specified sample size is reached. Researchers then examine the data and determine the next action – typically, to continue to the next phase or to stop the trial.

Phase I is a safety study comprising a small number of people (typically 6–80) and run over months to determine a safe dosage range and identify side effects.

In **Phase II**, a cohort of up to several hundred is typically split into two groups, with one group receiving a placebo. The phase aims to evaluate a drug's potential efficacy and to continue gathering information on its side-effects.

Phase III trials study a drug's efficacy in groups from several hundred to several thousand by comparing it to another current or experimental treatment. At the completion of the phase III trial, a potential treatment can seek regulatory approval.

Phase IV trials are conducted after the treatment has hit the market to continue to monitor its effectiveness and, often, to compare it to an already available treatment.

Then, in 2014, the Platform for European Preparedness Against (Re)-Emerging Pandemics was looking for consortia focusing on pandemic preparedness, and offering significant funding for everything from laboratory work to community engagement and surveillance. The group put in a bid and were funded to the tune of $6 million, with Steve Webb the only non-European principal investigator.

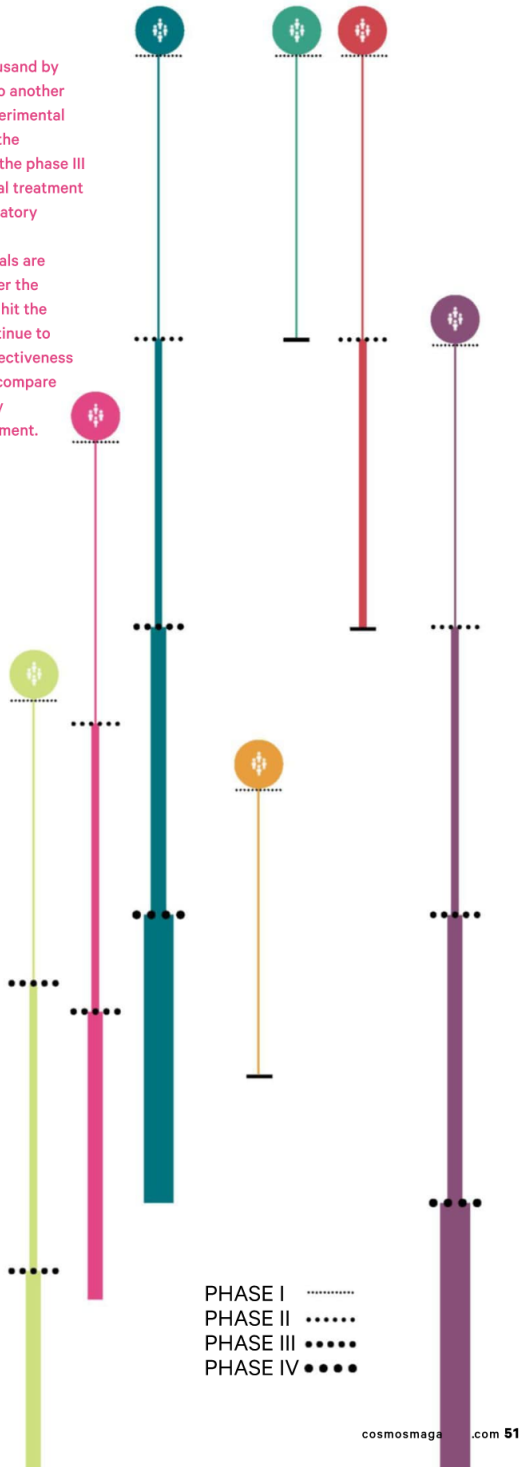
The REMAP-CAP trial (Randomised, Embedded, Multifactorial, Adaptive Platform for Community Acquired Pneumonia) was born.

A year later Australia's medical research funding body, the National Health and Medical Research Council, provided an additional $4.4 million funding. The Canadian Institutes of Health Research and the Health Research Council of New Zealand followed, largely through the efforts of the other co-lead of REMAP-CAP, Colin McArthur, Director of Research at Auckland City Hospital.

"By 2017 we had core funding for the program," Webb says. "So, we started to build what would become the world's most complicated clinical trial."

It took a long time for the group to write the protocol for REMAP-CAP. The team had to work out how to collect data and evaluate the eligibility of patients in both quick and easy ways.

"Staff in ICUs are already stretched – we didn't want them to be burdened further by making the process of registering a patient into a REMAP-CAP trial too difficult," Webb says. "We wanted to keep the process to between five and seven minutes, which is no more than an ordinary clinical trial."



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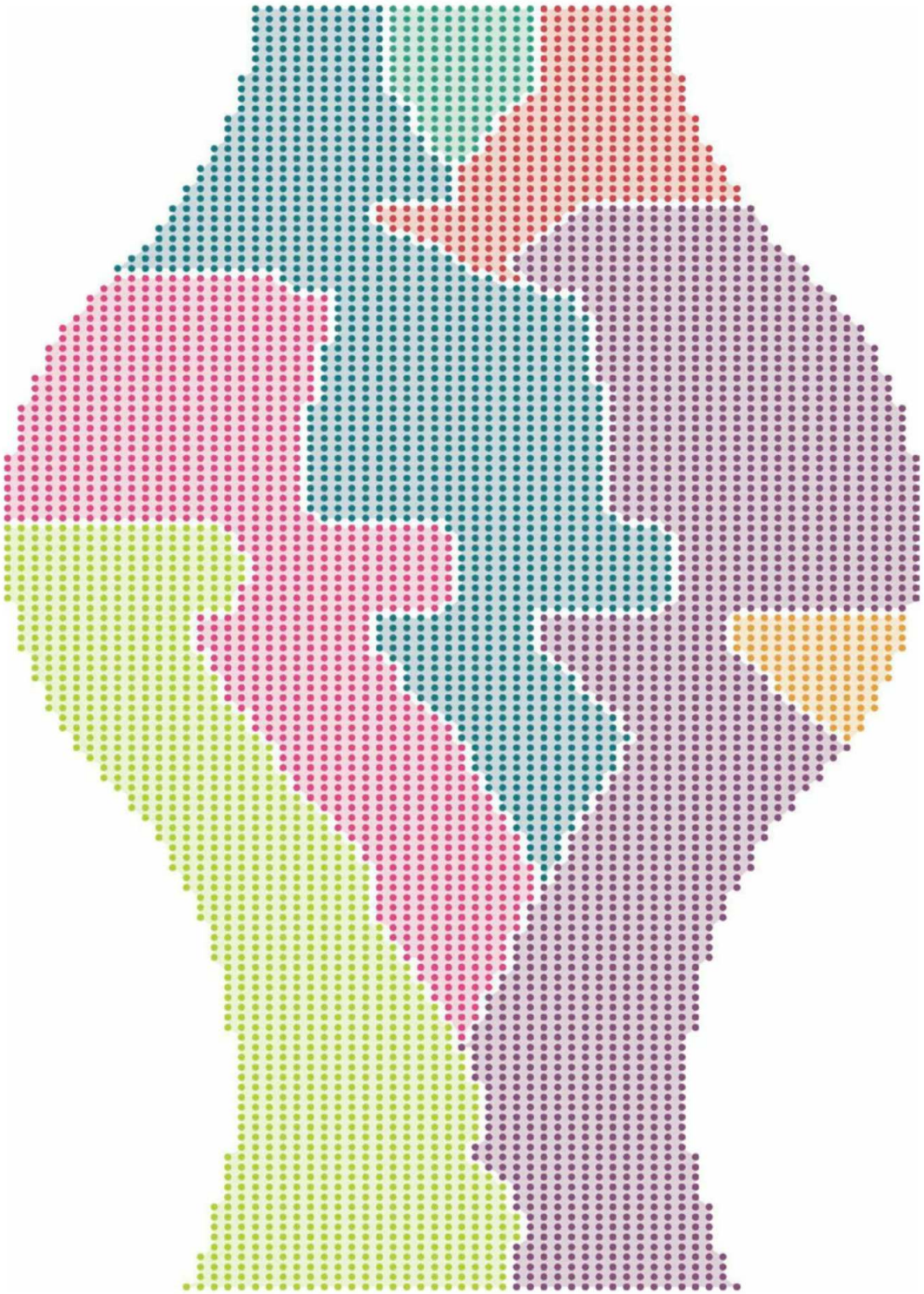

By 2019 more than 50 hospitals in more than a dozen countries were participating in REMAP-CAP, looking at treatments – antivirals and antibiotics – in Australia, New Zealand, Canada and Europe on people in ICU with community-acquired pneumonia. There had been some moments of concern that a pandemic had already arrived: 2012 saw the MERS virus outbreak, and then in 2015, Zika. Despite initial alarm, neither became global threats.

REMAP-CAP had reached what Scott Berry calls "sleeping mode": recruiting CAP patients, still working out operational issues but effectively ready to go.

Or so they thought. In December 2019 came reports of a new respiratory disease in Wuhan, China. "But we still thought it was more likely to be another MERS or Zika," Scott Berry recalls.

By January 2020 reports were escalating that the virus was spreading rapidly and causing high morbidity. "It started to be a real thing then, a real risk that this was the pandemic we had expected" Berry says. "We still weren't sure, but we shifted staff and thought, let's get ready."

In London on 17 January 2020, Steve Webb received an email from Antwerp University's Professor Herman Goossens, the coordinator of PREPARE, the EU organisation that was the first to provide funding for REMAP-CAP. "He said that his contacts had warned him of a person-to-person transmission of a pneumonia-causing virus in Wuhan in China, which meant this could be the 'big one'," Webb recalls.

The REMAP-CAP team started flipping the small number of global sites they already had gathering CAP data into getting ready for what they feared would be an influx of people, "even though at that stage we weren't sure that the disease would spread outside of China or even outside of Wuhan", Webb says.

> "People were coming into ICUs in severe respiratory distress, and we neither knew what was causing it, beyond a form of flu, and more importantly we didn't know how to treat it"

Scott Berry
President & Senior Statistical Scientist, Berry Consultants LLC

The confusion surrounding the H1N1 pandemic occurred because of the sudden influx of people with CAP into ICUs in the early days of the pandemic. "People were coming into ICUs in severe respiratory distress, and we neither knew what was causing it, beyond a form of flu, and more importantly we didn't know how to treat it," he recalls.

Because REMAP-CAP sites globally were already evaluating the use of corticosteroids on bacterial pneumonia, the team woke up the sleeping pandemic stratification in the protocol for the Wuhan disease, as it was then known.

REMAP-CAP recruited its first COVID patient on 10 March, the day before the WHO declared the SARS-Cov-2 virus a pandemic.

The pandemic no one wanted (but had been planning for)

By definition, pandemics are unpredictable and emerge suddenly. So REMAP-CAP's premise – to have a protocol and infrastructure in place in order to generate critical evidence, efficiently, about optimal treatment so that clinicians and policy makers can utilise that information to improve patient outcomes – seems challenging, to say the least.

Traditional clinical trials just don't work in a pandemic. Conventional trials are a fixed design, comparing treatment A with treatment B, with no capacity to change the treatments or sample size or even analyse the results until recruitment is complete. The static and rigid design of these trials simply didn't meet the needs of a global disease that would be filling hospital ICUs. The REMAP-CAP team had learnt this back in 2010 and 2014.

At the beginning of the COVID-19 pandemic, numerous potential treatments emerged to assist those who were the sickest. Suggestions ranged from the head-lice treatment ivermectin, to bleach, steroids,and to plasma from those who had recovered. Some of these things may have proved helpful, others may have been harmful – but until and unless these treatments were randomised, it would just be guesswork. Regardless of the number of doctors and healthcare workers observing improvements due to one treatment over another, without randomisation these observations would remain anecdotal – an unreliable way to guide treatment.

ADAPTIVE TRIAL

In an adaptive trial, continual data analysis allows researchers to assess the efficacy and safety of multiple treatments in real time. Unlike a standard clinical trial, participants can continue to join the study, and data analysis will randomise them towards more beneficial treatments. Adaptive trials improve health outcomes for participants, avoid ambiguous results, and can end when sufficient data have accrued rather than when a pre-specified sample size is met.

The example at left takes the same trials as on the previous page. Patients are progressively randomised into three initial treatments. Data is collected and analysed continuously. As the green is shown not to be beneficial, randomisation proportions are updated and future participants are randomised towards the blue and red treatments.

Research continues. New treatments are added for trial (purple and pink). More data results in more knowledge: less beneficial treatments dwindle as randomisation proportions are updated.

Lime green is an example of an innovation on the pink treatment, which is showing benefit. The innovation is a success, and supersedes the pink, which although successful has less efficacy than the subsequently developed treatment.

As this moment in time ends, beneficial treatments have large numbers of participants without having sacrificed the important safety steps that a clinical trial provides, while less beneficial treatments aren't required to play out a costly and time-consuming phase.

The United Kingdom was one of the first countries outside of China to be swamped by COVID-19. The REMAP-CAP program was selected as a national priority trial on 1 April by chief medical officers across the UK. Most ICUs took part, enrolling patients who were admitted for treatment in intensive care. The UK's National Health Service (NHS) already had an embedded research arm in its hospital system with paid research coordinators who facilitated the uptake of the REMAP-CAP protocols.

"These research coordinators were taken off the trials they were on – cardiovascular, cancer etc – and suddenly we had an enormous number of patients enrolling into a whole series of investigational treatments, literally just months into the pandemic," Webb says.

A key to the REMAP-CAP program is that once a treatment is looking favourable it's randomised into the treatment of more patients, effectively speeding up the learnings of the clinical trial. Information from patients already participating in the study is used to help guide the treatment of new patients joining the study. Under REMAP-CAP, as a therapy sees positive results a higher proportion of participants receive that treatment, and fewer participants are randomised to those treatments that are performing poorly.

Colin McArthur
Director of Research, Auckland City Hospital

"We had become a factory for generating results and, as soon as we had a result that was statistically significant, we would publish, which was always the aim of the project."

REMAP-CAP global project manager Cameron Green joined the team in 2019, shortly before the COVID-19 pandemic, because he was impressed with the novel design of REMAP-CAP and its Bayesian model, "which ensured that any patient enrolled in a trial would have the benefit of the evidence that had already been accrued, when in normal trials that's not the case", he says.

The inclusion criteria for any of the REMAP-CAP trials aimed to be both broad and blunt: an adult admitted to ICU because of the pandemic disease and requiring some form of organ support. Success was a simple measure: the reduction in deaths during the hospital admission and, in survivors, a reduction in the number of days receiving life-sustaining treatments in an ICU.

With more than 150 UK hospitals on board with another 70 hospitals in Australia and New Zealand, more ICU sites joined across Europe and Canada, and in late 2020, Pakistan, India and Nepal. Later participants included Japan, Singapore, South Africa and Malaysia. But only a few hospitals in the US joined REMAP-CAP – constrained by the very high costs of trials in the US and complex regulatory environment. The University of Pittsburgh Medical Center, with its multiple ICUs, recruited many patients while covering its own costs.

Overseeing it all was Cameron Green, based at Monash University, liaising with international trial coordinators, regional coordinators, statisticians and database providers, adding new domains as new treatments needed testing and working on contracts with every ICU that came on board.

"All the time we wanted to make it easy for the ICU staff to enrol patients, so we worked tirelessly to make the process seamless, because without the ICU staff on board we would never have managed," he says.

In Australia the philanthropic Minderoo Foundation boosted funding for REMAP-CAP, "because it revolutionised the global treatment of COVID-19 in critically ill people in an incredibly short timeframe", according to Dr Steve Burnell, who led Minderoo's COVID-19 response.

Webb says that Minderoo's foundational funding, made early in 2020, was pivotal in the platform's rapid expansion and global impact – especially during the pandemic's critical early phases, before vaccines were available and when so many people were dying from COVID-19 infection.

By mid-2020, REMAP-CAP was joined by other large clinical trials looking at COVID-19 therapies and treatments. The UK's Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial was ward-based and instrumental in finding cheap and effective COVID-19 treatments, though its funding ran out in October this year. In March 2020, the WHO undertook Solidarity, a large, simple, international, open-label, randomised trial in patients hospitalised with COVID-19, looking at the efficacy of drugs like Remdesivir. In the US, the National Institutes of Health conducted, and continues to conduct, trials for the treatment of COVID-19.

According to Steve Webb, only the RECOVERY trial – with its platform also evaluating multiple treatments – was similar to REMAP-CAP, but it focused on patients in hospital wards, while REMAP-CAP studied the very ill in ICUs.

"The two trials worked in tandem to give us a hugely important overview into what treatments work for all patients sick enough with COVID that they were hospitalised," he says.

By the end of the COVID-19 pandemic's chaotic first year, a writing team within REMAP-CAP started to publish. In preparation for the massive amounts of meaningful information that needed to be relayed to clinicians, the team had developed a template that could be completed quickly, with data, methods and discussions and rapidly sent off to major journals like the *Journal of the American Medical Association* (*JAMA*) and *NEJM*.

Along the way, the REMAP-CAP platform utilised information from other trials to adapt what they would study. In June 2020, REMAP-CAP stopped collecting data that evaluated corticosteroids and hydroxychloroquine; the study's first results, published in September, provided confirmatory evidence on the effectiveness of corticosteroids.

In December 2020 REMAP-CAP released research showing that the interleukin-6 inhibitors, tocilizumab and sarilumab, were an effective treatment, including in patients who had been receiving corticosteroids. This result was communicated to the clinical community through an announcement by the then UK Prime Minister, Boris Johnson.

Two days before Christmas 2020, REMAP-CAP sent out an alert that they had paused the use of blood thinners for critically ill COVID-19 patients. Three clinical trial platforms worked together to combine their data on blood thinners, to learn more efficiently that COVID-19 patients in ICU did not benefit from, and were possibly harmed by, anticoagulation drugs.

In February 2022, a landmark paper published in *NEJM* revealed, via REMAP-CAP data, that the use of tocilizumab and sarilumab in COVID patients in ICU led to an 8% reduction in mortality. By this stage, REMAP-CAP had 10 full-time statisticians undertaking analyses that were packaged rapidly for publication in medical journals.

"We had become a factory for generating results and, as soon as we had a result that was statistically significant, we would publish, which was always the aim of the project," Webb recalls.

At its height, REMAP-CAP was running at 360 ICU sites. Since the beginning of the pandemic, the REMAP-CAP team have published eight papers on the treatment effect of 11 different treatments, and have randomised 11,700+ patients. Another three papers covering four treatments are currently being prepared.

What's the next pandemic going to be?

As COVID-19 deaths remain high globally but the world seems to be living with the virus, REMAP-CAP is now transitioning away from the pandemic – although they continue to recruit COVID-19 patients to study new or repurposed treatments as they are developed.

Instead, given the rise of non-COVID respiratory illnesses and pneumonia globally – particularly as the Northern Hemisphere heads into what's predicted to be a harsh and wet winter – REMAP-CAP is continuing to study community-acquired pneumonia.

According to Webb, the REMAP-CAP program is heading back to "sleeping mode" – but with a caveat. Over the past 300 years there has been an influenza pandemic on average every 23 years; swine flu in 2009 was the most recent one.

Street art by Kai 'Uzey' Wohlgemuth in Hamm, western Germany. The text reads: For the real heroes.

Cameron Green
Global Project Manager for the REMAP-CAP trial

"So we are due another pandemic in the next 10 to 20 [years]," Webb predicts.

While COVID wasn't an influenza strain, its impact on the respiratory system was profound, which made REMAP-CAP so relevant. Historically, the pandemics that kill the most people are respiratory pandemics, so efforts like RECOVERY, with its funding cut and trial disbanded in October 2022, and REMAP-CAP – still funded by the EU, New Zealand, Australian and Canadian governments – are not planning on being "retired".

Scott Berry says that COVID has forever changed the way we deal with disease. "Those lessons and these platforms will be used in the next pandemics, our understanding of what pandemic preparedness means has changed," he says.

"We need to continue the urgency for the treatment of non-pandemic diseases that we showed during the pandemic. We have to always be ready to go, we have to be able to pull the rip cord on these trials immediately."

Whatever comes next, "REMAP-CAP is ready". ●

TANIA EWING is based in Melbourne. This is her first story for *Cosmos*.