UK achieves site activation world record for Roche during COVID19 pandemic

Speed is of the essence in the race to understand which treatments and vaccines can help to solve the worldwide COVID-19 challenge. The UK's rapid response to this urgent public health crisis has been applauded by global life science company, Roche, as the international COVACTA study achieved its recruitment target.

COVACTA evaluated the safety and efficacy of tocilizumab in patients with severe COVID-19 pneumonia. Tocilizumab is an immune modulating drug which has been used to treat inflammatory conditions such as rheumatoid arthritis for almost a decade. The team at Roche was quick to respond when they saw a signal from the drug when it was used in Wuhan, where the initial outbreak of COVID-19 occurred. Rav Seeruthun, Medical Director for Roche UK during the trial, explains what happened next:

"After we saw the initial signal in Wuhan, we began to see tocilizumab being used in Italy and then in Spain. Immediately we wanted to make sure that this drug was rigorously investigated to ensure it was safe to use in patients with this very new disease, and to get a definitive answer to the questions: which COVID-19 patients might benefit from tocilizumab? And to what extent do they benefit? Consequently, COVACTA was planned as a pivotal, placebo controlled trial in nine countries*; one of which was the UK."

In the UK a single, collective system-wide approach has been established to prioritise and expedite research relating to COVID-19. It involves multiple organisations including: the National Institute for Health Research (NIHR); Public Health England; UK Research and Innovation; the Health Research Association (HRA); and the Medicines and Healthcare Products Regulatory Agency (MHRA), among others. This collaborative way of working has resulted in a number of nationally prioritised COVID-19 studies being initiated in record time.

Cross sector collaboration

COVACTA was badged as an Urgent Public Health Research on 26 March, Rav Seeruthun describes the impact of this priority status on the set-up of COVACTA at a national level:
"The first thing we did was call the MHRA. They immediately connected us to the NIHR and NHS England, who then brought the relevant people together to come up with a strategy for rapidly trialling tocilizumab across the UK. I think it's the first time that I've seen academia, government agencies, pharmaceutical companies and groups like the NIHR come together so rapidly in a way that really puts patients first.

"The alignment between all the different agencies worked incredibly well. Everything was expedited, processes were streamlined, and approvals were executed in parallel. Usually approvals for a study can

* Denmark, France, Germany, Italy, Netherlands, Spain, UK, USA, Canada

take three to six months, especially in big complex studies. But these were happening in record times. The MHRA was responding to submissions in 48 hours. It was astounding."

At the same time Jonathan Sheffield, NIHR COVID-19 Research Operations Director, ensured that the Roche team was connected with clinical academics from the University of Oxford and Imperial College London who are leading two platform trials that were already underway in the UK.

"We were already having initial discussions regarding the REMAP-CAP trial with Tony Gordon at Imperial, but RECOVERY wasn't front of mind", explains Rav Seeruthun. "It was great that the NIHR, through Jonathan Sheffield, were able to pull all of the pieces together. It meant that, in addition to COVACTA, we could explore if tocilizumab could help a broader range of patients, in different settings." Jonathan Sheffield explains how RECOVERY and REMAP-CAP presented opportunities for both patients and for Roche:

"Roche colleagues have been exceptional. Firstly they have been extremely cooperative around COVACTA to get sites open and avoid delays. Then, once they saw how our Urgent Public Health Research Response had accelerated the set-up of COVACTA, and how well the UK was recruiting, they ensured multiple doses of tocilizumab were available for both the RECOVERY and the REMAP-CAP platform trials. This means that more UK COVID-19 patients are getting access to a potential treatment. It's this level of collaboration and commitment that will help us to beat this virus."

Record breaking site activation

Meanwhile, as work commenced to add tocilizumab to the two platform trials, the COVACTA study was breaking Roche world records for speed of site activation. Dr David Harland is the UK liaison for the COVACTA study. He experienced the same level collaboration at site level:

"The sites, the NIHR, Roche and PPD colleagues are all fully committed to solving the global COVID-19 challenge - this was clear from study set-up, right through to recruitment. Everyone was available, accessible and transparent every step of the way. We were able to pick up the phone to anyone we needed to speak to, at any site, at any time. That was partly because of the collective commitment to the cause and to an important study, but also because COVACTA had the NIHR Urgent Public Health prioritisation stamp on it. We were able to overcome barriers in hours that might normally take weeks, or even months, to solve."

This led to incredible recruitment statistics. Firstly the UK reached its initial recruitment target of 36 patients in two weeks. Then, following this exemplary performance, the UK was asked to continue recruiting and also to open two additional sites to further support global recruitment. Dr David Harland continues:

"The other stand out feature was the speed at which we were able to activate those additional sites. We went from initial discussions with University College London Hospital to activation in four days, which included a weekend. Then St George's University Hospital was activated in just three and a half days. We started discussions with the site on a Tuesday and they recruited their first patient on the Friday afternoon which, again, is absolutely phenomenal performance.

"Another example of how well COVACTA was supported, is that we really wanted to support recruitment over the weekend. One of the sites expressed concern about staff availability for recruitment - which is understandable during a pandemic. Within an hour of speaking with the NIHR Local Clinical Research Network team we had NIHR research nurses allocated to support the study over the weekend."

Some COVACTA sites were also supporting delivery of RECOVERY and REMAP-CAP. For the Roche team, COVACTA had to be the priority because it was the label-enabling study. Again, the NIHR supported delivery by liaising with those sites to ensure COVACTA maintained the same high-priority status as the other studies. As a result, some sites adopted a co-enrollment strategy and a handful of patients took part in two, or even all three, trials. Dr David Harland added, "It is not an understatement to say that having the NIHR prioritisation was absolutely critical to making COVACTA a success in the UK."

COVACTA also was supported in all nine countries by PPD, a leading global contract research organisation (CRO). David Johnston, Ph.D., PPD's executive vice president of clinical development, said some amazing feats were accomplished for Roche's critically important study:

"Everyone involved in this study understood the urgency, which led to a strong strategic partnership. In most cases, sites randomised their first patient within one or two days of being activated, while in one instance, a site was initiated and activated, then enrolled its first patient all on the same day. The patient recruitment results also were exceptional, taking just seven days from the ethics committee's approval to the first-patient-in milestone. Rapid site activation and patient enrolment require efficient coordination between the CRO, the investigator sites, ethics committees and the study sponsor. The outcomes achieved in this study demonstrate what's possible when you have that alignment and teamwork."

COVACTA achieved its global target of 450 patients. The UK was the second highest recruiting country, second only to the USA. Eight UK sites recruited a total of 68 patients in seven weeks - almost double the number of patients projected, and double the number of patients recruited by the third highest recruiting country. As we look to the future one question that everybody is asking is: what can we learn from this?

"I think it's around maintaining these links that have been made," says Rav Seeruthun. "We saw everyone pulling together in the same direction, and that was because there was a huge societal need. The important thing now is that those transparent, pragmatic conversations continue to happen for all disease areas, not just Covid-19, to ensure that new treatments are available for those who need them. COVID-19 has been a catalyst that has shown what we can achieve together, providing a blueprint for how we should collaborate in future so we can help people live longer and healthier lives."

The science: why Tocilizumab was seen as a potential treatment for COVID-19

When the COVID19 virus invades a cell in the respiratory tract it injects its own genetic material (called RNA) so that it can take over control of the functions of the cell and begin replicating by the millions. This triggers the infected cells to send out messenger proteins, called cytokines, to raise the alarm and

call in immune cells to fight the infection. The immune cells arrive on the scene and then go through the same process, releasing their own cytokines, to call for reinforcements.

For the majority of people this chain reaction works well to clear the virus from the body. But for some, the immune system goes into overdrive and the production of cytokines spirals out of control. Excess cytokines begin to overload the system, blood begins to clot, vessels begin to leak, fluid begins to form in the lungs (pneumonia) and breathing difficulties develop. This overreaction is known as a 'cytokine storm' and is now widely believed to be the root cause of the most severe respiratory complications that are associated with COVID19. Then, with the immune system malfunctioning at a critical level, other organs in the body are at risk of damage or even failure, causing death.

Cytokine storms are not unique to COVID19. Some blood cancers, sepsis and auto-immune disorders such as lupus are known to trigger a cytokine storm. Consequently, clinicians know that, in order to control the most severe COVID19 infections, we must find a way to control the immune system response.

Some cytokines appear to perpetuate the storm more than others, one of which could be a cytokine called interleukin-6. Tocilizumab is a humanized (synthetic) monoclonal antibody which has been developed to suppress the interleukin-6 cytokine. By using tocilizumab to target this cytokine the hope was that we can slow the chain reaction, calm the storm, and work towards restoring a normal immune response.