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THE HINDU EXPLAINS

Relevant for: Developmental Issues | Topic: Health & Sanitation and related issues

The story so far: On Saturday, the University of Oxford and AstraZeneca said they were resuming clinical trials for a new coronavirus vaccine across all U.K. sites. On Tuesday, the U.K.-based biopharma company AstraZeneca had said it was suspending the Phase-3 global trial of AZD1222, the COVID-19 vaccine it has been developing with Oxford University researchers. The vaccine, by all accounts, was among the handful that had reached the final but most daunting stage of trials and is slated to be available commercially by mid-2021. The pause was announced after a volunteer in Britain fell ill. On September 12, Oxford University and AstraZeneca in separate releases said the independent review process had concluded and following a nod from the regulator, trials would resume in the U.K. There was no word in the releases about resumption of global trials or details of the volunteer's illness.

There are similarities and differences in the way new drugs and vaccines are tested. Broadly both follow a four-stage process when they are tested in people. After a drug has proven itself safe in a variety of animals — usually mice, rabbits, hamsters and primates that mirror human physiology and the way it reacts to diseases — it enters Phase-1 studies. A small group of volunteers is given the drug in small doses and monitored to see if it is safe and whether it was well tolerated. This is also when any occurrences of side effects are closely monitored. On an average, 10-50 candidates are chosen. In the normal course, those undergoing the trial must report results to the drug regulator which gives the go-ahead for the next stage of trials. Phase-2 is when a group of volunteers, usually in the hundreds, are selected. This is the stage when researchers try to determine what dosage would be necessary for it to take effect or produce the desired response. In the case of the COVID-19 vaccine, this is the stage when it's determined if the inoculation had triggered a desired level of antibodies and a sufficient cell response in terms of stimulating T-cells that are known to block and neutralise the virus particles respectively. Again, side effects and adverse reactions are monitored and reported.

Comment | The participants we need in Phase 3 trials

Each of these stages can take several months and that includes the time taken to recruit patients as well as the time involved in observing the effects of drugs and vaccines at various intervals of time. Such data is again sent to regulators, who, if satisfied, give the green signal for Phase-3. In this stage, the drug or vaccine is tested at multiple locations in thousands of volunteers or patients. In the case of a drug, this is the stage when a new drug is compared to the existing standard of care and when it must prove that it is either more efficacious, or is of similar potency but is safer, better tolerable or delivers any of the goods that the drugmakers had claimed when making the drug. In the case of a vaccine for a new disease, there is usually nothing to compare it to, so Phase-3 becomes a larger version of the Phase-2 trial. A Phase-3 trial is held at multiple locations to capture the demographic variability in the population. It is also double-blinded and randomised and may have multiple treatment arms, meaning some participants may get a placebo, some may get lower doses, some higher doses, and in an ideal trial, neither the doctor nor the recipient knows who is getting the drug and who the placebo. When the scale and scope of a trial increases and a diverse population group is exposed to a new vaccine, the odds of encountering adverse and the dreaded 'severe adverse reaction' are magnified. When severe reactions are manifested, medical researchers have to determine if the reaction was due to the drug and if a pattern is apparent, a drug or vaccine can be pulled out. Because of the multiple locations and the number of patients that are required, this is also the most expensive stage of a trial. Sometimes, phases are combined, given the kind of drug or vaccine and the urgency of the situation. Several COVID-19 vaccines are being developed on

accelerated time lines.

For the vaccine candidate, called AZD1222 for now, the company had begun recruiting 30,000 volunteers for Phase-3 trials in the United States. The Pune-based Serum Institute of India, which had been contracted to manufacture a hundred million doses for 92 countries including India, had also started to test the vaccine on a proposed group of 1,600 volunteers in India. However, it emerged that a recipient of the vaccine in the United Kingdom contracted transverse myelitis, an inflammation of the spinal cord, and this led AstraZeneca to pause its trials. Suspension of vaccine trials is not out of the ordinary but Serum Institute initially said it would not halt the India trial because no adverse reactions had been reported here. However, after a show-cause notice from the regulator, the Drugs Controller- General of India, the company said it would halt recruitment of volunteers until AstraZeneca finishes evaluation of the safety data.

Comment | More than a vaccine, it is about vaccination

According to a release from Oxford University, the independent review process has concluded and following the recommendations of both the independent safety review committee and the U.K. regulator, the MHRA (the Medicines and Healthcare products Regulatory Agency), trials will restart in the U.K. “We are committed to the safety of our participants and the highest standards of conduct in our studies and will continue to monitor safety closely,” the release said.

Coronavirus | Oxford vaccine trial pause a wake-up call: WHO Chief Scientist Soumya Swaminathan

A drug or vaccine candidate that clears Phase-3 is usually approved and licensed and the entire infrastructure of the company is devoted to ramping up production and working out the logistics of storing the drug or vaccine safely without it degrading or losing potency. Once the product goes out into the field, there is post-marketing surveillance, or a Phase-4, where all instances of the product’s failure and adverse events are recorded. Companies are expected to furnish periodic data to the drug regulator.

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