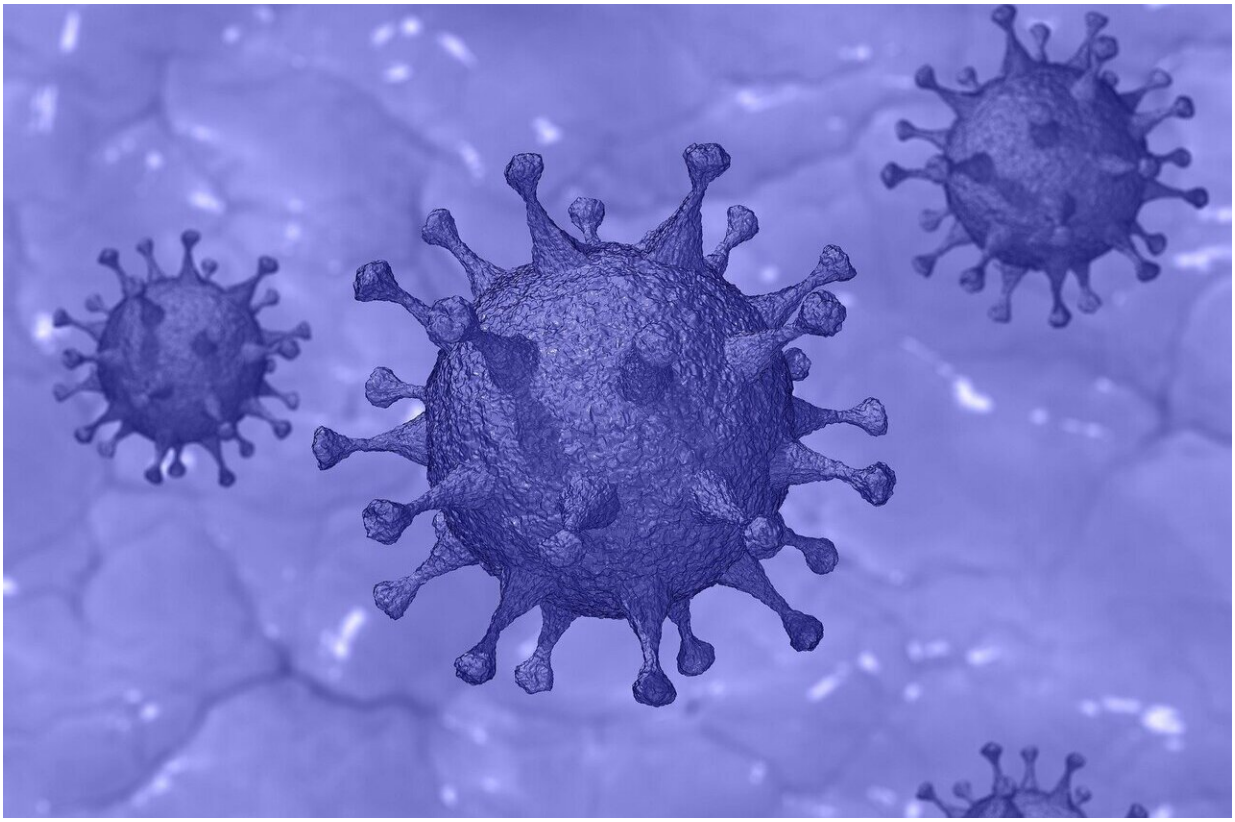
Why halting the COVID-19 vaccine trial is part of the process

September 10 2020, by Shabir Madhi



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This week the University of Oxford and Astra Zeneca temporarily postponed further vaccination in clinical trials of the COVID-19 candidate vaccine, AZD1222, after one of the participants fell ill. There

are more than 15,000 participants already enrolled across multiple studies of the vaccine in several countries around the world, including 1,800 in South Africa. The Conversation Africa's health and medicine editor, Ina Skosana, asked Professor Shabir Madhi, who is leading the South African leg of the trial, what these developments mean for the search for a vaccine.

Why was the trial suspended?

Pausing enrolment into a clinical trial is not unusual or unique to the COVID-19 vaccine. It happens often in the early phases of clinical development of investigational vaccines and other therapeutics, when there's uncertainty as to the safety profile. For a COVID-19 vaccine to be licensed and recommended for use, it must be proven to be safe.

The decision to suspend trials came after one of the study participants in the United Kingdom experienced a medical event. The recommendation was made by the data and safety monitoring committee, which is independent of the investigators, and based on the stringent protocol criteria under which these studies are being conducted. The committee wanted to interrogate this particular medical event in more detail to determine whether it might be related to the participant having received the COVID-19 vaccine that is being evaluated.

In the clinical studies, participants receive either a placebo or control-vaccine, or the COVID-19 vaccine. The data and safety monitoring committee will be able to determine which of these the participant was allocated to. The committee—made up of clinicians, epidemiologists, and vaccinologists from the UK, as well as South Africa—will determine if this particular event might biologically be related to the participant having been vaccinated with the COVID-19 vaccine, or if there is another explanation for the event.

What are the next steps?

For the trial, the next step is for the data and safety monitoring committee to conclude whether this medical event might be related to vaccination.

The committee would also consider the severity of the episode. Even if the event were related to vaccination, the committee would need to judge the risk benefit profile of having other participants continue receiving the vaccine.

Many of the participants enrolled in South Africa have already started to receive the second dose of the vaccine or placebo. But we've suspended vaccination for those who were scheduled for a second dose. We'll wait for the committee's findings and recommendation as to whether and when vaccination can be re-initiated.

This interruption in completing enrolment into the study, as well as delays in administering the second dose at the scheduled time, is unfortunate. But it is necessary because the safety of the participants is of paramount concern to us. Should the data and safety monitoring committee allow the study to continue, it will likely set back the completion of the study by the equivalent of the period during which the study has been paused. But this interruption is unlikely to affect the integrity of the findings of the study.

What would it take for the trial to resume?

The decision to resume a study depends on the data and safety monitoring committee's assessment. The committee has the prerogative to pronounce on this and, to a large extent, the investigators need to adhere to the committee's recommendation.

We'll also need the data and safety monitoring committee's recommendations to be communicated to the local regulatory authorities. In South Africa this would include the University for the Witwatersrand and University of Cape Town Ethics Committees and the South African Health and Related Products Regulatory Authority. They will be engaged prior to further vaccination of study participants taking place in South Africa.

Only after that is done will we resume vaccination of participants. Those who are already enrolled into the study will continue with their routine scheduled visits, and will continue to be evaluated for COVID-19.

What also happens in studies of this nature is that if more participants experience medical events similar to those that resulted in the hold on further vaccination, those cases will also be reviewed by the data and safety committee in real time.

What about the other COVID-19 vaccine trials taking place in South Africa?

The Oxford vaccine is a different vaccine construct than the other vaccine that is being evaluated in South Africa. It's a vector based vaccine, which is a different technology than that used for the vaccine developed by Novavax, which is the other vaccine being evaluated in South Africa. The Novavax vaccine is based on a more traditional approach of using only a protein (the spike protein) of the virus. These vaccines may also induce different immune responses.

There are a number of other vaccines also in clinical evaluation in other countries. Enrolment into those studies continues. Each of these studies has its own data and safety monitoring committee, which monitors—in real time—any serious adverse events that might be occurring. It's a

safeguard that is put into place to ensure the safety of participants. This is of paramount importance to the investigators as well as to the companies that are developing these vaccines.

So what were're experiencing with the Oxford vaccine and the measures put into place is not unusual. Many phase one and phase two clinical trials have holding rules. And if those holding rules are met, it requires a review by the data and safety monitoring committee to make a decision as to whether the risk benefit profile is in favor of ongoing evaluation.

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