Data and safety review board reports how it monitored the COVID-19 vaccine trials

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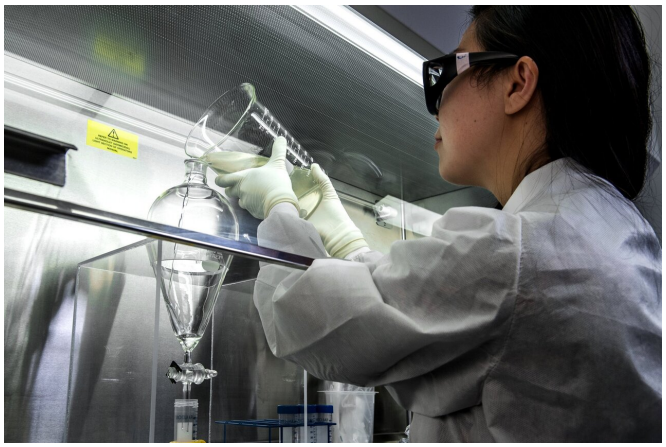

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Clinical evaluation of three COVID-19 vaccine candidates in 2020-21 during a worldwide pandemic that killed or sickened millions was unprecedented in terms of urgency and scope. Responsibility for the safety, integrity and scientific validity of the trials in the United States fell to 12 experts of the federally appointed COVID-19 Vaccine Data and Safety Monitoring Board, or COVID-19 DSMB, who in turn report to an oversight group.

This COVID-19 DSMB team—which included co-contributing author Richard Whitley, M.D., distinguished professor of pediatrics in the University of Alabama at Birmingham School of Medicine—has now taken the unusual step of publishing details of their review process in *The Journal of Infectious Diseases*.

Their goal, they say, is to assure the public of the board's independence and lack of interference from external actors, while they operated under exceptional conditions. Challenges the board faced included:

- The remarkable scale and pace of the trials.
- The frequency of safety events among a combined enrollment of more than 100,000 people, many of whom were older adults or persons with comorbidities that put them at independent risk of serious health events.
- The need to monitor a portfolio of related trials rather than a single trial, and the need to harmonize these studies.
- The politicized setting in which the trials have taken place, including a United States presidential election.

Despite these challenges, they say that the COVID-19 Vaccine DSMB also "can serve as a model for future situations in which there is an urgent need for coordinated development of multiple therapeutic or preventive interventions to address rapidly evolving public health threats."

The story began in May 2020, as the federal government launched Operation Warp Speed to accelerate COVID-19 vaccine development. The operation included funding for multiple large randomized trials to assess the safety and efficacy of candidate vaccines and agreements to purchase hundreds of millions of doses to assure timely manufacture of ample quantities of vaccine.

To ensure rigorous, independent and unbiased scientific and ethical oversight of the vaccine field trials, the National Institute of Allergy and Infectious Diseases, or NIAID, empaneled the COVID-19 Vaccine DSMB. The board has 11 members from the United States, Brazil, South Africa and the United Kingdom, including experts in infectious disease, vaccinology, immunology, biostatistics, pharmacoepidemiology, public health and bioethics, as well as a biostatistician, who is a full-time NIAID employee and serves as executive secretary.

The DSMB's *Journal of Infectious Diseases* article details their study review process as they reviewed

three formal interim efficacy analyses of trials for vaccine makers Moderna, Janssen and AstraZeneca. The board currently is monitoring the Moderna, Janssen, AstraZeneca and Novavax trials. The trial of the Pfizer/BioNTech vaccine, which was not federally funded, has a separate DSMB.

The DSMB reports that it has met by videoconference more than 25 times, generally for two to three hours at a time. As needed, the board holds ad hoc meetings to address emerging safety concerns. If accrual or event milestones were met between scheduled meetings, the board met to review interim analyses.

The board focused on trial conduct, safety and vaccine efficacy. This included a close look at accrual of trial participants, including the numbers and proportions of people in relevant subgroups like age, sex, race, ethnicity and people with risk factors that predispose them to severe COVID-19.

"The DSMB's role in overseeing a portfolio of multiple trials," the board writes, "has facilitated its ability to perform safety monitoring across all trials. For example, when concerns first surfaced about thromboembolic events associated with AstraZeneca's vaccine in Europe, the DSMB was able to review relevant categories of adverse events across its portfolio of trials to look for broader patterns associated with SARS-CoV-2 vaccines as a class."

Participant safety was a central responsibility for the board, which devoted much attention at each meeting to review interim safety metrics. Given the large number of participants in the trials, the board also received regular reports of individual adverse safety events between meetings and determined what further information or actions in response might be needed.

Among the political challenges the board faced was what *Science* magazine called its "extraordinary rebuke" last March, when the board said the company had used potentially misleading and outdated data in its initial analysis.

The highly politicized atmosphere also included an August 2020 tweet by then-President Donald Trump that the United States Food and Drug Administration "deep state" was delaying COVID-19 vaccines, and his September suggestion that a vaccine for COVID-19 could be ready by Election Day. Another political challenge came when then-FDA Director Stephen Hahn said he was prepared to authorize a vaccine before Phase 3 trials were complete.

Yet politics did not affect the board's work. In its report, the COVID-19 Vaccine DSMB concluded that "Operation Warp Speed is an unprecedented effort to develop safe and effective vaccines that will help end the COVID-19 pandemic.

"Conducting clinical trials under these circumstances requires the utmost attention to participant safety and to data integrity, so that the public and the medical community will ultimately have trust in the vaccines and the process used to develop them. Although (the board) operates behind the scenes, by virtue of its access to unblinded interim data, its charge to recommend changes to ongoing studies based on these data, and its ability to examine emerging data across multiple parallel trials, the COVID-19 Vaccine DSMB is uniquely positioned to ensure that these goals are met."

More information: Steven Joffe et al, Data and Safety Monitoring of COVID-19 Vaccine Clinical Trials, *The Journal of Infectious Diseases* (2021). DOI: 10.1093/infdis/jiab263

Provided by University of Alabama at Birmingham