

## Behind the Scenes Heroes: the COVID-19 Vaccine Data and Safety Monitoring Board

Lawrence Corey<sup>1</sup>

<sup>1</sup>Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, WA

Lawrence Corey  
1100 Fairview Avenue North  
Mail stop E3-300  
Seattle, WA 98109  
[lcorey@fredhutch.org](mailto:lcorey@fredhutch.org)  
206-667-6770

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This issue of *the Journal of Infectious Diseases* publishes an important article by Joffe et al that identifies the people, mission, and workings of the Data and Safety Monitoring Board (DSMB) established by the National Institute of Allergy and Infectious Diseases to oversee the United States government's COVID-19 vaccine program (ref Joffe et al). The article is a beautifully understated way of explaining the Board's charter and responsibilities but, most importantly, the workings and enormous responsibility of this committee. By way of full disclosure, I was one of the people who felt a single independent DSMB was an essential requirement for the framework of utilizing independently conducted harmonized clinical trials to evaluate COVID-19 vaccines. We did so for reasons the authors articulated in the article to "facilitate informed judgments about the interim analysis;" to provide an independent evaluation of adverse events and, perhaps most importantly, that individual trials would benefit from insights from the complete trial portfolio (ref 2). These statements and the rather dry comment that the group met once a week for two to three hours and ad hoc as needed are major understatements of the effort and wisdom required to perform these tasks.

The COVID-19 vaccine trials that the DSMB oversaw were remarkable in their size and pace. Each trial enrolled from 30,000 to 45,000 persons in 8-10 weeks; on some days, over 2000 persons were enrolled in a single trial (refs 3-5). The entire country participated in the program, and between 90 and 140 clinical trial sites were utilized for each trial. The trials were staggered at a pace of essentially one 30,000-person trial per month and, hence, as of today, the Board has under review 4 30,000-45,000 persons trials with another scheduled to start in late May 2021 (refs 3-6). Each trial is designed to go for 24 months and, therefore, their job will not be over until late 2023 (ref 7). The trials, while designed to be streamlined, were far from simple, for COVID-19 is not a simple disease. Independent medical evaluation was performed for each case of COVID-19 acquired during the trials. Each person with COVID-19 was followed daily, including monitoring of their pO<sub>2</sub> by pulse oximetry to define the clinical spectrum and severity of each person with COVID-19. The amount of

data accumulated was enormous and the DSMB reviewed it all. Ad hoc meetings of the committee were frequent.

Because of the extensive outbreak of COVID-19 that occurred in the US during the time frame in which the trials were conducted, the trials finished a full two months sooner than the estimated time to arrive at the 150-case primary analysis. When one enrolls and follows 30,000 persons during an epidemic, one goes from 150 to 400 cases of COVID-19 in the blink of an eye, even if the acquisition rate is 2% of enrollees every 6 months. Strain variation added to the complexity associated with the trials. But even more importantly than these scientific complexities was the public scrutiny of the trials and the DSMB. Articles in the press about the trials were present in the mainstream media nearly daily and the polarized setting of the trials due to the politics of the Trump administration raised the newsworthy profile of the entire program. The label “Operation Warp Speed” didn’t help. Would the trials reach their endpoint prior to the election? Would science and data be manipulated prior to the election? These were part of the daily dialogue associated with the trials and the de facto decisions being left to these eleven members of the DSMB.

The article describes the workings of the Board. The member insights are helpful, but I sure most of us would like to know even more. Were there things the DSMB would have changed and, if so, how might those have helped the outcome? Were they comfortable with the processes and procedures under which they worked? What would be best practices for future epidemics? Should one common DSMB continue to be utilized? What were the areas that they felt were most insightful in which cross trial knowledge was an important component in decision making or in guidance of the second vaccine company after what was learned from the first? What is the workload compatible with optimal accuracy and were there tensions about any decisions that were made? The trials were constructed so that the companies own the data because it was felt that would speed application to the FDA. Was this the optimal system? Should the role of academia have been greater in the decision-making and/or conduct of the trial? The trials brought together a research alliance between

academia and the pharmaceutical industry. Not only did academia participate, but so did the citizens of the country. The successful trials enrolled a racial diversity of participants not previously seen with any large set of clinical trials in such a short period of time (ref 8 Andrasik et al).

The data from the trials have formed the basis for the remarkable vaccine rollout we are now experiencing. This DSMB was central to all of these events. Perhaps this article will initiate some future dialogue about the issues outlined in the prior paragraph. I hope such deliberations occur. What is certain now is how central this group of colleagues were to the success of the COVID vaccine clinical trials enterprise. To paraphrase Winston Churchill, we would say, “Never have so many of us in investigative medicine owed so much to so few.” (ref 9)

All of us should thank these men and women who assisted in this effort; we owe them our gratitude.

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