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CLINICAL TRIALS CASE STUDY

Monitoring Multiple U.S. Government–Supported Covid-19 Vaccine Trials

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Introduction

Chana A. Sacks, M.D., M.P.H., Editor

On March 11, 2020, the World Health Organization declared Covid-19 a global pandemic. The causative agent, SARS-CoV-2, has generated infections in more than 500 million persons and resulted in more than 6.5 million deaths worldwide, making it the worst pandemic in more than a century. From the beginning, it was clear that the rapid development of effective vaccines would be crucial for pandemic control. In May 2020, the U.S. government launched Operation Warp Speed (OWS), a partnership among vaccine companies, government agencies, and academia,[1] to accelerate the development of Covid-19 vaccines. A fundamental element of OWS was that the National Institutes of Health (NIH) would constitute a single data and safety monitoring board (DSMB) to review and monitor all federally funded OWS vaccine trials. As members and the executive secretary of the DSMB, we describe here the unique issues and challenges faced and offer suggestions for future similar endeavors.

DSMBs are used routinely in NIH- and industry-sponsored trials.[2-5] Our DSMB was composed of clinical research experts, biostatisticians, and an ethicist. DSMB members were independent of the organizations and institutions sponsoring the clinical trials and of the teams conducting them. We reviewed unblinded data as trials progressed and were charged with making recommendations, such as modifying or stopping a trial early for efficacy, futility, emergence of new/competing changes in standards of care, or harm.

Scope of the DSMB Work

We monitored five phase 3 randomized trials of vaccines developed by Moderna, AstraZeneca, Johnson & Johnson, Sanofi/GlaxoSmithKline, and Novavax (Table 1 and Fig. 1). Pfizer-BioNTech did not participate in OWS-supported vaccine development, and thus our board did not provide oversight of the Pfizer-BioNTech vaccine trial. Because most trials ran concurrently, and there was little early-phase safety data on the vaccines, we reviewed safety data often during the early months of each trial. This required an intense meeting schedule with close to weekly meetings for more than 1 year.

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Company	Vaccine Platform	Trial Size — No. of Participants
Moderna	mRNA	30,420
Johnson & Johnson	Replicating defective live adenovirus vector	39,321
AstraZeneca		32,449
Novavax	Recombinant subunit adjuvanted proteins	29,960
Sanofi/ GlaxoSmithKline		21,046

Table 1. Vaccine Trials Monitored by the Data and Safety Monitoring Board.

Unique Aspects of the Covid-19 Vaccine DSMB

REPORTING STRUCTURE

For NIH-sponsored trials, the DSMB serves in an advisory role to the NIH, communicating major recommendations to NIH leadership for acceptance or rejection. OWS was a collaboration between the pharmaceutical companies making the vaccines, the Biomedical Advanced Research and Development Authority (BARDA), and the NIH. The pharmaceutical companies were the regulatory sponsors, operational coordinators, and partners in protocol development. BARDA, a government agency responsible for the procurement and development of medical countermeasures against health threats such as emerging diseases, provided funding for these vaccine trials, and the NIH provided scientific leadership during protocol development and throughout the implementation of the trials. Because these three groups needed to be part of major decisions for each trial, a novel structure was created to receive the recommendations from our board. A distinct three-member oversight group that included a representative from the company making the vaccine, the NIH, and BARDA was formed for each of the five trials. Each DSMB meeting included three sessions with different attendees joining us — open (trial team), closed (unblinded statisticians and independent unblinded clinician), and executive (no additional attendees). After these three sessions, we met with the oversight group and presented our recommendations. In some cases, there was discussion or clarification of the recommendations. We later provided a formal summary of the recommendations to the oversight group, which either accepted, modified, or rejected the recommendations. As the regulatory sponsor, the company had the final say in decisions, with the NIH and BARDA providing input.

The agreement by the NIH to give the ultimate decision-making authority to one member of the oversight group, the regulatory sponsor, led to some tense interactions with

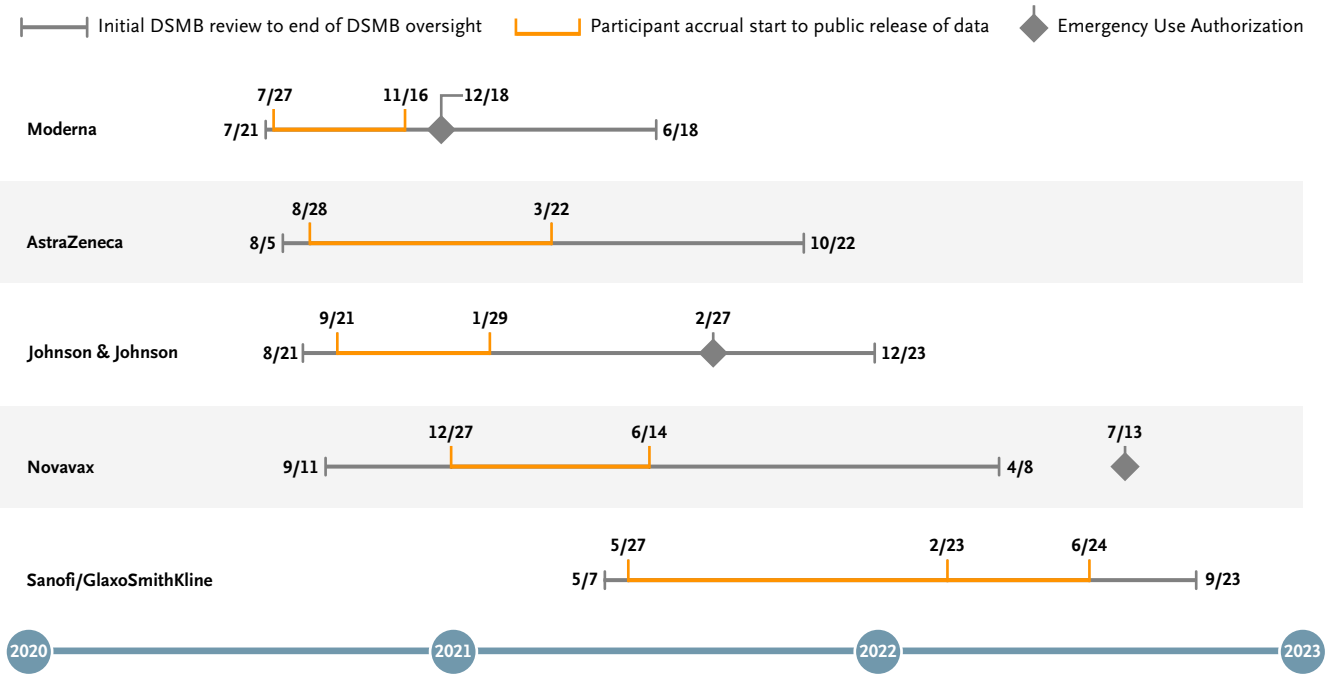

Figure 1. Timeline for Monitoring of Operation Warp Speed Covid-19 Vaccine Trials.
DSMB denotes data and safety monitoring board. In the figure the black numbers represent month/day of the noted year.

the companies. Many of us have served on other NIH DSMBs, and thus we anticipated that the relationship between the sponsor and the decision-making process would be in line with the usual practices for NIH DSMBs — that is, when NIH receives recommendations, they either follow a DSMB's recommendation or have discussions with the DSMB until consensus for a path forward is reached. The vaccine companies did not always follow this approach. For example, some press releases were issued that presented early results but did not include the caveats regarding the data that we had recommended.[6,7]

MEDIA ATTENTION

Given the pandemic's impact on morbidity and mortality and its disruptions to life, there was a strong imperative for the rapid development of effective vaccines. The stakes were high on multiple fronts to swiftly achieve this important objective. Although the goal of our work was clear — to save lives — our work occurred amidst a complex landscape. Motivations for rapid vaccine development among stakeholders included the potential return to normalcy for society, the political impact of an effective vaccine in an election year, and the billions of dollars from sales of an effective vaccine. There was concern expressed in the media that scientific rigor would not be upheld during this accelerated vaccine development and regulatory review, because of pressures to deliver a vaccine. To address this skepticism, OWS leadership assured the scientific community and the public that an independent group of scientific experts, the DSMB, would be the only ones to review accumulating data and recommend an early trial halt if scientifically and ethically warranted.[8,9] This brought us to the unique position of conducting confidential deliberations while receiving broad media attention.

Although the NIH did not disclose the names of DSMB members, we were allowed to publicly disclose our own membership on the DSMB if we wished, but we were asked not to disclose the identities of other members. Initially, we felt that anonymity would allow us to better maintain independence and the freedom to express our honest opinions during meetings; however, after the release of trial results showing the efficacy of the Moderna vaccine (the first trial under the board's purview to release its results), media attention lessened, and we decided to release our names and provide transparency by describing our board structure and conduct but not our deliberations.[10]

CONCURRENT MONITORING OF SIMILAR TRIALS

For NIH-sponsored trials, there is precedent for one DSMB to monitor several trials. For example, the Division of AIDS has three DSMBs that monitor HIV/AIDS trials, and the National Cancer Institute has a DSMB for each National Cancer Institute–supported cancer cooperative group, each monitoring trials of treatments and preventive strategies for a variety of cancers. Our portfolio of trials was different from these models because we monitored concurrent trials of vaccines for the same disease in the same population. This arrangement allowed us to monitor all trials for similar safety events and to apply lessons learned from one trial to the others. For example, the board carefully monitored the occurrence of Guillain–Barré syndrome, thrombocytopenia, thrombotic episodes, and myocarditis across all trials as these events were of special interest, either because of historical issues with other vaccines or because of events emerging in one of the Covid-19 vaccine trials or after deployment. Because we were evaluating all the trials, consistent scientific rigor was administered across all. Although knowledge of data from the different trials was beneficial, we were careful not to reveal confidential information about one company's vaccine to other companies.

Several vaccines received emergency use authorization (EUA) at different points in time (Fig. 1); therefore, we needed to consider the impact on ongoing trials if participants dropped out to receive a vaccine with EUA. For example, the Johnson & Johnson, AstraZeneca, and Novavax trials were ongoing when the Moderna and Pfizer-BioNTech vaccines received EUA. Because it was in the best interest of trial participants to receive an approved vaccine as soon as they were eligible, we advocated for trial staff to encourage participants to receive vaccines, even if this created difficulties in the interpretation of trial results. Because of the reactogenicity of the vaccines, trial participants may have concluded that they had received vaccine or placebo on the basis of symptoms that developed after receiving the trial product, raising the possibility of unequal dropout or right censoring from trial arms. We therefore monitored dropout rates closely for any indication that dropout was affecting the interpretability of trial data.

Challenges

HARMONIZATION OF TRIALS

We faced many challenges as a result of the unique aspects of the OWS trials (Table 2). Along with a common DSMB for all vaccine trials, a fundamental OWS principle was to ensure harmonization across vaccine trials.

Table 2. Summary of Challenges, Their Impacts, and Corrective Actions Taken or Could Be Taken in the Future.*

Challenge	Negative Impact	Corrective Actions Occurred or Suggested Future Solution
Different trial protocols with different core fundamentals: • End point definitions • Eligibility criteria • Visit schedules • Data collection methods • Seropositivity tests	Cross-trial differences in vaccine efficacy could be a result of differences in trial protocols	Specify common core fundamentals across trials† Harmonization of primary end point and introduction of a secondary end point with identical definition of symptomatic Covid-19 in all protocols‡
Different stopping boundaries for efficacy	Confusion if trials stopped using different levels of evidence	Agreement among OWS and company leadership on similar stopping boundaries‡
Companies held and controlled trial databases	Follow-up analyses by independent groups delayed or not performed	Agreement up front that independent contributing groups, such as the NIH and academia, have access to data in a timely manner†
Pressure for early interim reviews	Reviewing incomplete data could lead to inconsistent results	DSMB must adhere to statistical principles when performing interim analyses†‡
Duration of trial monitoring by the board	Duplicative effort; once data are unblinded, FDA or study teams can perform review	End involvement when trial results were reviewed by the FDA‡

* DSMB denotes data and safety monitoring board; FDA, U.S. Food and Drug Administration; NIH, National Institutes of Health; and OWS, Operation Warp Speed.

† Suggested future solution.

‡ Corrective action occurred.

An optimal strategy would have been to have all protocols share common primary end point definitions, eligibility criteria, visit schedules, data collection methods, and seropositivity tests. Unfortunately, because of differing practices and preferred contractors of the involved companies and the urgency of initiating trials, which precluded prolonged negotiations with each company, we could not achieve complete harmonization.

Some differences among trials were more important than others. The two most important were the different definitions of a symptomatic Covid-19 case — the primary end point for each of the trials — and varied stopping boundaries (trials could stop early with different amounts of information or different strengths of evidence). Typically, consistency across trials would not be a concern for a DSMB, as sponsors determine end points for their trials based on the preliminary data, clinical relevance, and what they believe is achievable. Guidelines for early stopping are usually set by the company and are based on several considerations that must be weighed together. The criteria must balance the desire for precise estimates of efficacy and safety, which require large numbers of participants, and the desire for an answer as early as possible so that a beneficial vaccine could be available for broad use. Early decisions are necessarily based on a reduced data set, and estimates of effects will accordingly have less precision. In this situation, with the stakes and interest high for all parties, including companies, government agencies, policymakers, and the public, we believed it was extremely important to require the same end point to determine benefit and the same level of evidence for all the vaccines to declare efficacy. We were concerned about the potential weakening of public confidence in the scientific process if different levels of evidence were used to determine efficacy and stop a trial. We did not want to allow for the possibility of questions being raised about whether favoritism was shown to one vaccine or company over others.

Because these were overarching concerns for all trials rather than a protocol-specific concern, we asked for a meeting with OWS, NIH, and BARDA leadership. We reached a consensus that the NIH would ensure that all trial protocols during protocol development included similar primary end point definitions and monitoring boundaries and that a secondary end point with an identical definition of symptomatic Covid-19 would be included in all protocols.

DATABASE ACCESS

As trials proceeded and were completed, our DSMB, the NIH trial team members, and academic partners identified important issues that could be addressed by additional within- and across-trial analyses, including potential correlates of protection and subgroup analyses that could

suggest whether vaccine efficacy varied according to factors such as age, race, and comorbid conditions. Some of these analyses would have been valuable for understanding Covid-19 early in the pandemic. Similarly, we saw the potential opportunity to obtain information on background safety events and natural immunity by combining the placebo arms across the trials. Unfortunately, the databases were maintained and controlled by each company, and sharing was not a priority for the companies. As a result, these analyses were delayed or have yet to be performed.

RELEASE OF DATA

We were under pressure to review efficacy data as early as possible, reducing the time for board review and requiring balancing the two legitimate needs of having sufficiently complete data to ensure reliable decisions and the need for rapid determination of positive results.

After a determination of positive results, submission to the U.S. Food and Drug Administration (FDA) for formal regulatory review could begin.

The protocols specified that participants were to be observed for 2 years to obtain efficacy data and monitor long-term safety; however, because of the burden of Covid-19 cases, efficacy results were released for each trial within 6 months of initiation. Our role became less clear after the release of efficacy results. Observation of participants for safety continued, but maintaining blinded safety reports was no longer necessary. We recommended ending the monitoring role of the DSMB for a trial when the company filed with the FDA, as the FDA would provide independent review of all data from that point, and study team members could review safety events according to trial arm.

Lessons Learned

Having a single DSMB for OWS vaccine trials, however challenging, was essential, especially given the immense political pressure surrounding vaccine development during the pandemic. When we recommended early stopping for the Moderna trial, the first government-funded Covid-19 vaccine trial to release results, there was little questioning of this recommendation. The FDA's review of the data and resulting EUA for this vaccine were in line with our recommendation. We monitored for safety events, such as Guillain–Barré syndrome, myocarditis, thrombocytopenia, and thrombosis, across trials and facilitated rapid reporting of such events to the FDA.

The ability of the companies to release results to the public without approval by all members of the oversight group needs to be considered carefully in the future. Each member of the oversight group represented an entity with different concerns and motivations. The company's desire to present the vaccine in the best light may influence decisions regarding the publication of results. On two occasions, we expressed concern about the accuracy or completeness of findings reported in press releases, recognizing that later publications would likely include substantially different results. Early release of results that may change upon subsequent publication can lead to public confusion or distrust. Our experience taught us that press releases should be approved by the oversight group, rather than by the company alone, before dissemination.

The large databases from these trials could be evaluated for findings related to important public health issues. In the future, an upfront agreement to make databases publicly available in a timely fashion (with "timely" clearly defined), especially given the federal investment in the trials, would be in the best interest of public health.

The model we have described is challenging and requires a substantial time commitment from dedicated experts; however, when multiple parallel trials are conducted to urgently address a public health emergency, the need for consistency and the ability to apply insights across trials supports the use of a single DSMB. Government funding agencies, such as the NIH and BARDA, should use such a model if similar circumstances arise in the future.

Disclosures

Author disclosures are available at evidence.nejm.org.

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