DATA AND SAFETY MONITORING BOARDS FOR TRIALS OF COVID-19 VACCINES: THE CHALLENGES

Susan S. Ellenberg, Ph.D.
Perelman School of Medicine
University of Pennsylvania

Collaboratory Grand Rounds
March 5, 2021

Penn Medicine

COVID-19 VACCINE TRIALS

- Many candidate vaccines have been or are being (or will soon be) studied
- All randomized trials have DMCs/DSMBs (?)
- Several vaccine candidates are studied under the NIH umbrella
- Others are or will be monitored separately

THE NIH COVID-19 VACCINE TRIALS

- NIH is working with several vaccine manufacturers on their Phase 3 trials
- Each trial has a 3-member Oversight Group
  - NIAID
  - Biomedical Advanced Research and Development Authority (BARDA)
  - Manufacturer of the vaccine being studied
- A single DSMB, constituted in mid-2020, oversees all the trials and reports to that trial's Oversight Group
- The DSMB's Charter applies to all the trials

DSMB OPERATION

- Executive secretary in NIAID Biostatistics Branch coordinates meetings and additional communications as needed
- Initial meeting for each vaccine to discuss protocol and plans for interim and final analysis
- Each meeting will have open and closed sessions
  - Open session: company describes study progress, any emerging obstacles, overall adverse event experience, description of individual adverse events of concern
  - Closed session: independent statistical group presents efficacy and safety data, as well as study conduct issues, by unblinded study arm
- Minutes are prepared by Executive Secretary, sent for DSMB review and finalized with concurrence of DSMB

DSMB MEMBERSHIP

- 11 members
- Countries represented
  - US
  - UK
  - South Africa
  - Brazil
- Disciplines represented
  - Clinical infectious disease
  - Virology
  - Immunology
  - Epidemiology
  - Biostatistics
  - Bioethics

VACCINES MONITORED

- Moderna
- Astra Zeneca
- Johnson & Johnson
- Novavax
- (Sanofi)

WHAT IS NEW?

- Great sense of urgency?
- Multiple trials monitored by a single DSMB?
- Focus on representation of particular subgroups?
- Very large sample size?

WHAT IS NEW?

- Great sense of urgency?
  - At least as much urgency in early HIV/AIDS trials
- Multiple trials monitored by a single DSMB?
- Focus on representation of particular subgroups?
- Very large sample size?

WHAT IS NEW?

- Great sense of urgency?
  - At least as much urgency in early HIV/AIDS trials
- Multiple trials monitored by a single DSMB?
  - Fairly common now for clinical trials networks—cancer cooperative groups, AIDS Clinical Trials Group, others
- Focus on representation of particular subgroups?
- Very large sample size?

WHAT IS NEW?

- Great sense of urgency?
  - At least as much urgency in early HIV/AIDS trials
- Multiple trials monitored by a single DSMB?
  - Fairly common now for clinical trials networks—cancer cooperative groups, AIDS Clinical Trials Group, others
- Focus on representation of particular subgroups?
  - Many trials give attention to subgroups of particular interest
- Very large sample size?

WHAT IS NEW?

- Great sense of urgency?
  - At least as much urgency in early HIV/AIDS trials
- Multiple trials monitored by a single DSMB?
  - Fairly common now for clinical trials networks—cancer cooperative groups, AIDS Clinical Trials Group, others
- Focus on representation of particular subgroups?
  - Many trials give attention to subgroups of particular interest
- Very large sample size?
  - Other vaccine trials (e.g., rotavirus vaccine trials) have been even larger

WHAT ELSE IS NEW?

- All meetings via Zoom
- Probably only workable way in any case, given frequency of meetings
- This aspect works reasonably well

STILL…

- Taken together, the challenges of monitoring these trials go beyond anything in my prior experience

INITIAL CONCERNS

- NIH worried that the enormous public interest in these vaccines would lead to bombardment of DSMB members by journalists (and perhaps others)
- For this reason, names of DSMB members were not made public, nor were dates of scheduled meetings
- This turned out not to be an issue
- Also, some worried that politics would interfere and force trial results to be released before their time—that also didn't happen

MULTIPLE TRIALS

- I have served on other DSMBs monitoring multiple trials
  - National Surgical Adjuvant Breast/Bowel Project
  - Cancer and Leukemia Group B/Alliance Oncology
  - NIAID HIV Prevention Trials
- For these trial networks, the data management and statistical analysis were handled by a single entity—uniformity
  - Report format
  - Quality control procedures
- Presenting statisticians typically very familiar with the science and the data

MULTIPLE TRIALS

- Despite efforts to harmonize protocols across studies, differences remain
- DSMB has pushed for more harmonization, particularly with respect to endpoint definition

MULTIPLE TRIALS

- Presentations from the different independent statistical groups vary in format and in quality
- We have encouraged participation of a clinician independent of the study and the sponsor, in preparation of the interim reports
- Lags in obtaining serology and PCR results have impacted interpretation of interim results in some cases

URGENCY

- Early days of HIV/AIDS
  - Sense of urgency from affected community
  - Researchers subjected to personal attacks
  - DSMB felt strong sense of urgency
- COVID-19
  - "Affected community" is EVERYBODY
  - Attacks aimed at politicians and other decision-makers, not researchers
  - All involved in research, including DSMB, feel strong sense of urgency—while recognizing the importance of assuring safety

FOCUS ON SUBGROUPS

- Subgroup issues have been particularly important in COVID-19 vaccine trials
- DSMB monitors carefully for representation of subgroups of interest in trial participants
  - Age > 65
  - Black
  - Hispanic
  - Co-morbidities that may predispose to more serious disease
- Particular interest in vaccine efficacy in older adults
  - At greatest risk of severe consequences if infected
  - Weaker immune systems

RAPID ACCRUAL

- The rapid accrual has allowed minimal opportunity to implement changes in study conduct
  - Meeting 1: introduction to study
  - Meeting 2: possibly 10% enrolled
  - Meeting 3: could be 60% enrolled
  - Meeting 4: fully enrolled
  - Meeting 5: interim analysis

MEETING FREQUENCY

- Each study is reviewed at least once a month
- This means that DSMB meetings generally occur at least weekly
  - Additionally, frequent ad hoc meetings to discuss specific issues
  - Ad hoc meeting may be called if criteria for performing interim analysis are met between scheduled meetings
- Despite effort to standardize, there are differences among studies
  - Endpoint definitions
  - Adjudication procedures
  - Approaches to data presentation
- Creates challenges in interpreting data properly

HIV vs COVID-19

- The DSMB for NIH-sponsored AIDS trials met quarterly (with occasional ad hoc calls)
  - Two statistical/data management centers were involved, one for each of the 2 clinical trials groups
  - Both groups were at academic centers
- The COVID-19 Vaccine DSMB meets much more frequently
  - Different statistical/data management centers for each trial
  - All are commercial CROs

ADVERSE EVENT ASSESSMENT

- As for vaccine studies generally, safety considerations are extremely important
  - The entire global population will in principle be candidates for vaccination
  - Even extremely rare vaccine reactions will be important to know about
- Reports of new serious and unexpected outcomes are reported to the DSMB almost every day
- Determination of causality for individual events is typically difficult or impossible
- Particular attention to types of events that have been associated with vaccines in past
  - Anaphylaxis
  - Guillian-Barré and other neurological events

ADVERSE EVENT ASSESSMENT

- Older adults, especially those with co-morbidities, are at elevated risk of death
- Particularly difficulty to evaluate potential contribution of vaccine in such participants
- Typically more deaths in placebo arm because of deaths from COVID-19

ASTRA-ZENECA VACCINE

- The study we monitor is one of two large field trials
- Other trial was completed first, has already led to regulatory authorizations in other countries
- DSMB should have access to safety information from other trials

HARM MONITORING

- Attention to potential for "vaccine enhanced disease"
- This phenomenon has been seen previously for other vaccines (dengue, respiratory syncytial virus)
  - Vaccine may be protective overall but may lead to more serious disease in vaccinees who do get infected
- Careful review of most serious COVID-19 cases

EFFICACY ASSESSMENT

- Primary outcomes are not defined identically for all vaccine candidates
- Criteria for performing interim analyses not identical for all vaccine candidates
- FDA guidance regarding requirements for Emergency Use Authorization applies to all vaccine candidates

PRIMARY ENDPOINT DEFINITION

- Many components
  - Days past final vaccine dose
  - Nasal swab positivity at baseline
  - Serology at baseline
  - Nasal swab positivity at time of event
    - Local assay
    - Central assay
  - Symptom cluster
  - Saliva test positive
  - Adjudication by central committee

CHALLENGES WITH ONGOING STUDIES

- Trial participants are increasingly becoming eligible for vaccination with authorized vaccines
- May simply drop out
- May request unblinding
- One trial is implementing a "crossover" approach developed by NIAID statisticians
  - Offer opportunity to receive the other arm
  - If participant originally got placebo, will get active vaccine
- Not yet clear what the optimal analysis will be for those receiving other vaccines
- Another issue: fewer older subjects in later trials

CROSS-STUDY ISSUES

- One advantage of a single DSMB is to permit assessment of outcomes across studies
- Challenge: what outcomes are most relevant to all vaccines, which are different in ways that could have implications for adverse effects?
  - Platforms (mRNA vs human adenovirus vector vs chimpanzee adenovirus vector vs recombinant protein)
  - Adjuvants
- Many different safety outcomes to consider
- Challenge: real differences vs chance findings?

CROSS-STUDY ISSUES

- An important question is whether a correlate of immunity can be determined
- A reliable correlate will greatly simplify evaluation of additional vaccine candidates as well as modification of current vaccines
- This issue is not one that the DSMB will review

FINAL COMMENTS

- Monitoring any one of these trials would be challenging—monitoring all of them is HUGELY challenging
- There is a strong sense of urgency in making definitive results available as quickly as possible, but also a very strong commitment to make sure we are confident of the findings
- The companies have for the most part been very responsive to our recommendations
- The NIH coordination by the Executive Secretary has been essential