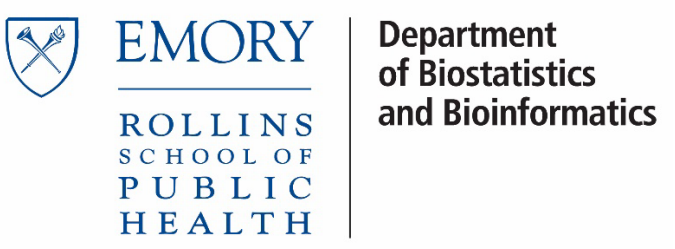

BIOS 522: Survival Analysis Methods

Activity 11:

Survival analysis in clinical trials

This week we discussed important key concepts in clinical trials. We then focused on sample size and power calculations for clinical trials with survival outcomes. We discussed clinical trial monitoring.

Problem 1. Moderna COVID vaccine protocol

For today's activity, we will answer questions about Moderna's pivotal Phase III COVID-19 vaccine efficacy trial protocol. The protocol is posted on Canvas. Answers to today's questions can be found within the following sections:

- Section 1.1 Synopsis (pp 6-17)
- Table 1: Objectives and Endpoints (pp 34-37)
- Section 9: Statistical Considerations (pp 83-98)

(a) Define the primary efficacy OBJECTIVE of the trial. (*What is the goal?*)
Define the primary efficacy ENDPOINT of the trial. (*How is it defined?*)
Define the primary efficacy ANALYSIS of the trial. (*How is it analyzed?*)

The primary efficacy objective is to demonstrate the efficacy of mRNA-1273 to prevent COVID-19.

The primary efficacy endpoint is first occurrence of COVID-19 starting 14 days after the second dose of the vaccine, where COVID-19 is defined as symptomatic disease based on the following criteria (at least two systemic symptoms OR at least one respiratory sign/symptom) AND positive RT-PCR.

The primary efficacy analysis: estimate VE as 1 – hazard ratio (mRNA-1273 vs placebo) using a Cox proportional hazard regression model with treatment group as a fixed effect and adjust for stratification factor based on the per

protocol set, with cases counted starting 14 days after the second dose of vaccine.

(b) What is the null hypothesis? Express this both in terms of vaccine efficacy and hazard ratio.

The null hypothesis is VE ≤ 30%, or equivalently, HR ≥ 0.70. The null hypothesis is not VE ≤ 0% or HR ≥ 1 because there is a higher threshold for use for a product (vaccine) that is given to healthy people.

(c) Describe the assumptions for the sample size calculations.

i. What is the smallest effect size they want to be powered to detect?
ii. What is the desired power?
iii. What is the type 1 error level?
iv. What is the required number of events?
v. What is the expected incidence rate in the control group?
vi. What is the expected dropout rate?
vii. What is the expected percent of the study population that will be excluded from the primary analysis?
viii. Approximately how many patients did they plan to enroll?

i. What is the smallest effect size they want to be powered to detect? 60% VE (0.40 HR)
ii. What is the desired power? 90%
iii. What is the type 1 error level? One-sided 0.025
iv. What is the required number of events? 151 COVID-19 cases
v. What is the expected incidence rate in the control group? 6-month incidence rate of 0.75%
vi. What is the expected dropout rate? 2% loss of evaluable participants
vii. What is the expected percent of the study population that will be excluded from the per protocol population? 15% (this includes people who are seropositive at baseline and who get infected before 14 days after the second dose)
viii. Approximately how many patients did they plan to enroll? 30,000

(d) Describe the interim-monitoring strategy and thresholds

This is described in section 9.6 and in Table 13. 2 planned interim analyses at 35% and 70% of total target cases across the two treatment groups. This is at approximately 53 and 106 cases. The nominal alpha levels are 0.0002, 0.0073, and 0.0227 at the first, second, and final looks. These alpha levels are based on the Lan-DeMets O'Brien-Fleming approximation spending function.

(e) Considering again the primary efficacy analysis. What type of test is used to test the null hypothesis? How are ties handled?

Two-sided score-based 95% confidence interval and 2-sided p-value.

Efron's method is used to handle ties.

This is described in Section 9.5.1.1.

(f) Did the investigators study severe COVID-19?

Yes. It is a key secondary endpoint. The definition of severe disease is defined on page 11 (COVID-19 plus high respiratory rate, low oxygen, acute respiratory distress, significant acute renal, hepatic or neurologic dysfunction, admission to the ICU or death). It was not the primary objective because it was relatively rare, and this would have required a much larger/longer trial.

(g) How did the study team guarantee that the trial included enough high-risk individuals?

Page 9. They stratified based on age and risk-status. There were 3 strata for randomization >= 65 years, <65 years but categorized to be at increased risk, and <65 years and not at risk. At least 25% of enrolled participants, but not more than 40%, will be either >= 65 years of age or <65 years of age and "at risk" of screening.

The vaccine was initially prioritized for approval high-risk individuals. They wanted to guarantee there was sufficient representation in the data for people who would be prioritized for the vaccine. They also wanted to generate more data on prevention of severe disease by including people at highest risk.

(h) How does the study team determine the time of the event? Describe how the patients are followed to assess their COVID status during the course of the trial.

P8. Surveillance for COVID-19 will be performed through weekly contacts with the participant via a combination of telephone calls and completion of an

eDiary starting at Day 1 through the end of the study. Participants with symptoms of COVID-19 lasting at least 48 hours (except for fever and/or respiratory symptoms) will return to the clinic or will be visited at home by medically qualified site staff within 72 hours (an “Illness Visit”) to collect an NP swab sample for RT-PCR testing for SARS-CoV-2 and other respiratory pathogens, or alternatively, if a clinic or home visit is not possible, will submit a saliva (or nasal swab) sample for SARS-CoV-2 RT-PCR testing.