INfluenza Vaccine to Effectively Stop cardio-Thoracic Events and Decompensated heart failure (INVESTED)

This exam is open-book but must be completed independently. You may not discuss the problems with anyone other than the instructor (lmao@biostat.wisc.edu).

The INfluenza Vaccine to Effectively Stop cardio-Thoracic Events and Decompensated heart failure (INVESTED) trial (http://www.investedtrial.org/) is a multi-center, double-blind, randomized controlled trial conducted between 08/2016 – 05/2020 across 180 sites in US and Canada, with the Data Coordinating Center (DCC) hosted by the BMI department at UW-Madison. The trial compared the effects of high-dose trivalent (n = 2,630) vs standard-dose quadrivalent (n=2,630) influenza vaccines on the morbidity and mortality of high-risk cardiovascular (CV) patients (3,773 men; 1,473 women; 14 other). The primary endpoint is time to the first of all-cause death or cardiopulmonary (CP) hospitalization, which showed no statistically significant difference between the two arms (Vardeny et al., 2021).

For the midterm exam, we analyzed the primary endpoint (i.e., time to the first composite event) against patient demographics and medical history as risk factors. In this final project, we further assess the effects of the treatment and risk factors on repeated CP hospitalizations and overall survival (i.e., death either before or after the first hospitalization).

The data are contained in `invested2.txt`, with the following variables:

`patid`: Patient identifier
`time`: Time (months) from randomization to death/hospitalization or censoring
`status`: 1 = hospitalization; 2 = death; 0 = censoring
`trtmnt`: Vaccine treatment (SD = standard-dose; HD = high-dose)
`gender`: Gender (Female; Male; Other)
`age`: Baseline age (years)
`race`: Race (White, Black/African American, Asian/Pacific Islander, Aboriginal/Native American, or Other)
`dbmi`: Body Mass Index
`lveflt40`: Current or historical LVEF < 40% (Yes or No)
`priormi`: Prior myocardial infarction (MI; Yes or No)
`priorhf`: Prior heart failure (HF; Yes or No)
`diab`: Documented diagnosis of type I or type II diabetes mellitus (Yes or No)
`renal`: Documented diagnosis of renal impairment (Yes or No)
`ischstr`: Documented diagnosis of ischemic stroke (Yes or No)
`pad`: Documented diagnosis of peripheral artery disease (Yes or No)

1. **Descriptive statistics:**

1.1 Tabulate the event rates by treatment group (SD vs HD) and overall for (1) death (overall survival); (1a) death before hospitalization; (1b) death after hospitalization; (2) first hospitalization; (3) recurrent hospitalizations. Comment on the results.
1.2 How many deaths/hospitalizations would be lost if we just focused on time to the first composite event (as we did in the midterm project).
1.3 Plot and compare histograms for the distribution of the number of hospitalizations per patient by treatment group. What percentages of patients are hospitalization-free; what is the maximum number of hospitalizations per patient in each group?

2. **Analysis of multiple/composite outcomes**
2.1. With death as a competing risk, estimate, plot and test the cumulative incidence function for the first hospitalization between the two treatment groups.
2.2. Analyze recurrent hospitalizations and death as separate endpoints.
2.2.1. Fit a multiplicative intensity frailty model for recurrent hospitalizations against the treatment and other risk factors (assuming death is independent of hospitalizations conditioning on the frailty, so it can be treated as censoring);
2.2.2. Fit a Cox model for overall survival with the same set of covariates.
2.2.3. Comment on the direction and magnitude of covariate effects on each endpoint.
2.3. [**Extra credit**] Analyze the treatment effect on the composite endpoints with death prioritized over recurrent hospitalizations using the restricted mean time in favor (RMT-IF) of treatment.
Hint:
1. You may need to consult the documentation, and examples therein, of the `rmt` package on the analysis of recurrent events and death;
2. You need to choose a reasonable restricting time τ and the maximum number K of recurrent events to consider (possibly using information from problem 1.3).

3. **Predictive modeling for the composite endpoint**:
3.1. Using the treatment variable and key risk factors, build a survival tree for the composite endpoint of hospitalization-free survival (i.e., time to the first composite event).
3.2. Based on the survival tree built in 3.1, plot the predicted hospitalization-free survival curves for two new patients, one treated with SD and the other HD, both:
female; 60 years old; white; BMI 25; LVEF < 40%; with prior histories of MI, HF, diabetes, renal impairment, ischemic stroke, and peripheral artery disease.

4. **Reporting:** Write a short paragraph (3—4 sentences) summarizing the most important findings of the analysis in the form of a press release for the mass media. Be certain to use concise, nontechnical language that would be understandable to a lay reader, while still accurate scientifically.

Reference:

Vardeny, O., Kim, K., Udell, J.A., Joseph, J., *et al.,* Solomon, S. D. (2021). Effect of high-dose trivalent vs standard-dose quadrivalent influenza vaccine on mortality or cardiopulmonary

hospitalization in patients with high-risk cardiovascular disease: A randomized clinical trial. *Journal of the American Medical Association,* 325, 39-49.