UPenn Conference: Comments on Afternoon Talks

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“If it ain’t easy, no one will use it”. Thanks to Terry for his survival R package!

Recommend really studying data after the primary analysis. Example....
Adaptive COVID-19 Treatment Trail (ACCT-1)

- Primary analysis: stratified logrank test on time to recovery in hospitalized COVID-19 (non-recovery and deaths censored at 29 days). Remdesivir increased recovery time compared to placebo. Highly significant. Beigel, et al, (2020).
Remdesivir Treatment Compared to Placebo Reduces the Rate of Clinical Deterioration

When examining the full trajectory of transitions between states using MSMs, we find that the rate of clinical deterioration within the hospital was lower among patients treated with remdesivir than those given placebo (Figure 2). Similar reductions in the rates of clinical deterioration within the hospital were estimated among patients receiving non-ICU respiratory therapies (HR, 0.74; 95% CI: .57–.94; \( P, .016 \)) and ICU respiratory therapies (HR, 0.73; 95% CI: .53–1.00; \( P, .05 \)) at baseline. We do not find evidence of a treatment effect on clinical improvement within the hospital. Although not statistically significant, the transition intensities leading directly to recovery were higher in the remdesivir arm than the placebo arm for patients receiving non-ICU respiratory therapies at baseline (HR, 1.19; 95% CI: .99–1.42; \( P, .064 \)), and the intensities of transitions directly to death were lower (HR, 0.56; 95% CI: .23–1.15; \( P, .099 \)). We do not find a similar pattern suggesting a multifaceted benefit among patients receiving ICU respiratory therapies at baseline.

Impact of Remdesivir Treatment in Patients Not Requiring ICU Respiratory Therapy at Baseline

The consequence of a lower rate of clinical deterioration within the hospital is a shorter course of hospitalization and a lower probability of requiring ICU respiratory therapies. Figure 3A shows the MSM point estimates of the expected ordinal scale distribution by treatment arm for patients receiving non-ICU respiratory therapies at baseline (OS 4 and 5). The expected percentages of patients in OS 6 to 8 (ICU states; orange and red bars) are higher in the placebo arm throughout the study period, whereas recoveries (dark blue bars) accrue faster among patients treated with remdesivir. At 1-week post-randomization, baseline OS 4 and 5 patients on remdesivir have better odds of being in improved states (Figure 3B; detailed results in Supplementary Table 5). This improvement in the overall odds of recovery and death persists throughout the study period, suggesting that remdesivir does not merely delay the inevitable.

The area of each state in the stacked probability plot corresponds to the expected total resource utilization for the clinical course of COVID-19 at the population level, conditional on the initial distribution of OS 4 and 5 patients. Based on this model, we expect that remdesivir treatment would result in fewer patients worsening to ICU-level care, reducing expected ICU resource utilization (Figure 3C). Our model estimates that treatment with remdesivir results in an expected savings of 21 ICU therapy days (95% CI: 5–38 days) per 100 patients admitted on room air (OS 4) at baseline, and a savings of 49 ICU therapy days (95% CI: 6–95 days) per 100 patients initially on supplemental oxygen (OS 5).
Clinical outcomes in patients receiving non-ICU respiratory therapies at baseline — ordinal scores 4 and 5

(A) Expected ordinal severity score distribution over the study period
Clinical outcomes in patients receiving ICU respiratory therapies at baseline — ordinal scores 6 and 7

(A) Expected ordinal severity score distribution over the study period

- Placebo arm
- Remdesivir arm

Clinical status:
- Recovery (1–3)
- Room air (4)
- Supplemental oxygen (5)
- NIPPV or high-flow oxygen (6)
- Invasive ventilation (7)
- Death (8)
Able to compare estimates of time in ICU for two arms.
Dr. Mao suggested two approaches to for constructing win ratio estimands:

- **Nonparametric (specify $\tau$):** Restricted WR: $\frac{w_1(\tau)}{w_0(\tau)}$

- **Semiparametric (proportional win-fractions model):** Assume $\frac{w_1(t)}{w_0(t)} = \theta$ for all $t$

- For a primary endpoint estimand, it seems like it is safer to use the nonparametric estimand, because it does not requires the proportional win-fractions model. Would one ever use a semiparametric estimand for the primary endpoint estimand?

- Nonparametric only requires independence assumptions on censoring to identify estimand. Seems like that is a less strict assumption than assuming proportional win-fractions.
Restricted mean time in favor

- \( w_a(\tau) \) defined differently than in win ratio
- \( w_1(\tau) = E(\text{amount of time in } (0, \tau] \text{ when treated is better than control}) \)
- \( \mu(\tau) = w_1(\tau) - w_0(\tau) \)
- Very nice easy to interpret estimand, and R package available.
Comments on Anne Eaton’s talk

- Beautiful idea
  - $P(D \geq t, Y(t) = 1) = P(D \geq t) \times P(Y(t) = 1 | D \geq t)$
  - $\hat{P}(D \geq t)$ with Kaplan-Meier
  - $\hat{P}(Y(t) = 1 | D \geq t)$ with kernel estimator

- Smooths out time to progression effect, so its effect is not so dependent on assessment visits
Comments on Anne Eaton’s talk

- Why use progression-free survival?
  - Progression is more common, effect easier to see.
  - Survival is more important, do not want to ignore it.
    (Do not treat death as censored!)

- Combining two endpoints does not help understand disease process better.

- Better for primary endpoint
Simple Example

- Interval censoring, twice as often in Trt B than in Trt A.
- Suppose progression-free survival and no one dies.
- What if treatment A is just a pain medication, so disguises pain, and you get assessed less often?
  - What is recommended in this case for a treatment effect estimand for progression-free survival?
  - If no deaths, then progression at observation time is invalid, but certain versions of logrank test are approximately valid (Fay and Shih, 2012).
Treatment A (assess every 20 days)

Survival

0 20 60 100
0.0 0.2 0.4 0.6 0.8 1.0

Treatment B (assess every 10 days)

Survival

0 20 60 100
0.0 0.2 0.4 0.6 0.8 1.0

Fay, Michael

Comments on Afternoon Talks
Event at First Observation of it
What if the assessment process depends on treatment? Talk about recommendations (Eaton and Zabor, 2022).
You recommend not making untestable assumptions. I would like to point out that we often assume independence of the censoring with the endpoint. Some assumptions are easier to accept than others.

“Clinical trials are not primarily designed to enhance understanding of causal mechanisms but rather to test and estimate effects on marginal process features and facilitate regulatory decision making.”

Restatement: Clinical trials are a robust (i.e., relatively model independent way) for establishing causal effects on populations, not for understanding causal mechanisms on individuals. In usual two-arm trial, each individual is observed only under 1 arm. Compare treatment effect on arms, not on each individual.
It was good to emphasize the problems with conditioning. That have been an issue with the usual proportional hazards model, and for this generalization it is good to mention the issue still applies!

Collider bias, and hazard of hazard ratios.

Example: Decreasing vaccine efficacy over time. Condition on being at risk for second half of study, then calculate vaccine efficacy for second part of study. Cannot interpret lower vaccine efficacy later to mean that the vaccine is losing its efficacy over time, could be that more frail/higher risk are eliminated early on from placebo arm.
Hazard ratios as estimands

- Hazard at any specific time is not a marginal estimand process feature, but ratio of cumulative hazards is a comparison of marginal process features (Vansteelandt, Dukes, Lancker, and Martinussen, 2022).

- Under proportional hazards assumption, that is a hazard ratio.
References


▶ Fintzi, et al (Clinical Infectious Diseases, 2022; 74(112):2209-17).