Special Considerations of Estimand Framework in COVID-19 Vaccine Trials

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Drouville, *In the fish tank*

Drouville is a patient, graphic designer and artist from Argentina who has survived multiple myeloma and a relapse.

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OUTLINE

1. **Definition of Estimands**
2. **Causal Estimands for Vaccine Efficacy in Prevention of Disease**
3. **Causal Estimands for Vaccine Efficacy Against Severe Disease/Death**

Treatments

Primary Efficacy Objective: to evaluate (demonstrate, estimate) the efficacy of the investigational vaccine in prevention of COVID-19

Astra Zeneca: 2-dose of ChAdOx1 nCov-19 (28 days apart) vs Placebo

Janssen: single dose of Ad26.COV2.S vs Placebo

Moderna: 2-dose of mRNA-1273 (28 days apart) vs Placebo

Pfizer: 2-dose of SARS-CoV-2 RNA (21 days apart) vs Placebo

Population

Astra Zeneca: Participants who receive at least 1 dose of study intervention excluding those participants who are seropositive at baseline, analyzed according to their randomized treatment.

Janssen: Participants who receive study vaccine and who are seronegative at the time of vaccination and who have no other major protocol deviations that were judged to possibly impact the efficacy of the vaccine.

Moderna: Participants who receive planned doses of IP per schedule and have no major protocol deviations, as determined and documented by Sponsor prior to DBL and unblinding, that impact critical or key study data.

Pfizer: Participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population

Variable

Astra Zeneca: First case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention.

Janssen: First occurrence of molecularly confirmed, moderate to severe/critical COVID-19 with onset at least 14 days post-vaccination.

Moderna: First case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 14 days after the second dose of study intervention.

Pfizer: First case of COVID-19 incidence based on central or locally confirmed NAAT occurring 7 days after the second dose

NB: Per Protocol (PP) analysis - the vaccine efficacy analysis will exclude all participants who experienced the endpoint within the first τ days

NAAT - *Nucleic Acid Amplification Test*

Summary Measure

There are three incidence measures of SARS-Cov-2 infection:

1. Cumulative incidence (attack rate): risk of a seronegative subject gets infected during a fixed follow-up period: π(T)=1-S(T) [S is survival function]
2. Incidence rate (infection rate): risk of experiencing an infection during a given time unit (week, month, or year): λ
3. Hazard rate (force of infection): $h(t) = \frac{-\partial S(t)/\partial t}{S(t)}$

Three definitions of Vaccine Efficacy:

1. VE=1- RR = $1 - \frac{\pi_v(T)}{\pi_p(T)}$, (assuming fixed period)
2. VE=1-IRR = $1 - \frac{\lambda_v}{\lambda_p}$, (assuming constant incidence rate)
3. VE=1- HR= $1 - \frac{h_v(t)}{h_p(t)}$, (assuming constant hazard ratio)

Intercurrent Events

1. Early COVID-19 event experienced within the first τ days after randomization;
   - $\tau = 14$ days after the 2 vaccination (AstraZeneca, Moderna)
   - $\tau = 7$ days after the 2 vaccination (Pfizer)
   - $\tau = 14$ days after the randomization (Janssen)

2. Missing dose of IP (adherence/compliance);

3. Seropositive at baseline;

4. Death unrelated to COVID-19;

5. Withdrawal from the study

Strategies for IE #1

- Per Protocol (PP) analysis - the vaccine efficacy analysis will exclude all participants who experienced the endpoint within the first τ days
  - Cannot rely on balance by randomization
  - If vaccine has a positive effect during the first τ days, the participants in the both treatment arm are not comparable
  - The resulting estimator is biased for the causal estimand

- ITT analysis - the vaccine efficacy analysis will include all randomized participants, irrespective of the time of experiencing the endpoint
  - Asymptotically unbiased answer to a question of clear interest
  - Doesn't take into consideration the fact that a vaccine may require some time to become effective
  - Proportional hazards assumption for the primary estimator should be questioned

- Principal Stratum (PS) – the vaccine efficacy analysis will include all randomized participants and will evaluate vaccine efficacy in the subset of population who would not experience the endpoint within the first τ days on both treatment arms

PS Estimand

- Let T be the random time from randomization until the Covid-19 disease event
- Let C be the censoring time, such that $Y=min(T,C)$ and $d=I\{T \leq C\}$ are observed on each participant
- Let A be an indicator of adherence/compliance to assigned treatment within the first τ days. We treat A as undefined if $T \leq \tau$
- Let Z be the treatment assignment: $Z=v$ or $Z=p$, for vaccine or placebo
- Let $\{T(z), C(z), Y(z), d(z), A(z)\}$ are potential outcomes of $\{T, C, Y, d, A\}$ under assignment $Z=z$ for $z=v$ or p.
- The PS cohort of interest is: $PS=I\{T(v)>\tau, A(v)=1, T(p)>\tau, A(p)=1\}$ :: subjects who would not experience the endpoint within the first τ days on both treatments and who would adhere/compliant to both treatments

Causal vaccine efficacy effect

- Define potential survival functions and hazard rates

$$S_z(t) = P(T(z) > t \mid T(v) > \tau, A(v) = 1, T(p) > \tau, A(p) = 1), for\ t \geq \tau$$

$$h_z(t) = -\frac{dS_z(t)}{dt} / S_z(t), for\ t \geq \tau$$

- Causal vaccine efficacy effect

$$VE = 1 - \frac{h_v(t)}{h_p(t)}$$

assuming constant hazard ratio after $t \geq \tau$

Alternative causal vaccine efficacy effect

- The PS cohort of interest is: $PS = I\{T(v) > \tau, T(p) > \tau, A(v) = 1\}$ :: subjects who would not experience the endpoint within the first τ days on both treatments and would be adherent/compliant under vaccine
- Define potential survival functions and hazard rates

$$S_z^*(t) = P(T(z) > t \mid T(v) > \tau, T(p) > \tau, A(v) = 1), for\ t \geq \tau$$

$$h_z(t) = -\frac{dS_z^*(t)}{dt} / S_z^*(t), for\ t \geq \tau$$

- Causal vaccine efficacy effect

$$VE^* = 1 - \frac{h_v(t)}{h_p(t)}$$

assuming constant hazard ratio after $t \geq \tau$

VE against severe disease / death

- Principal stratum (PS) of participants who would have experienced the COV-DIS endpoint under either assignment to vaccine or placebo
- Each participant has two potential SARS-CoV-2 infection outcomes:
  - S(v) = 1 or 0 and S(p)=1 or 0, if assigned to vaccine or placebo, respectively
- Each participant, if infected, has two potential outcomes of having severe disease/death:
  - Y(v) =1 or 0 and Y(p)=1 or 0, if assigned to vaccine or placebo, respectively
- Let $\pi(v) = \Pr(Y(v) = 1 \mid S(v) = S(p) = 1)$ and $\pi(p) = \Pr(Y(p) = 1 \mid S(v) = S(p) = 1)$
- Causal vaccine effect against severe disease/death in PS of “always infected” is clearly defined as:
  - $\Delta = \pi(v) - \pi(p)$

Motivation for PS Estimand

- Unsatisfied with the standard non-causal estimand that compares the post-infection outcome in the infected vaccine group versus the infected placebo group,
  - which could be particularly misleading because an effective vaccine could appear to harmfully increase the proportion of participants with severe disease/death

- The PS estimands restrict attention to a subgroup of scientific interest, namely those with no vaccine preventive effect on SARS-CoV-2 infection.
  - Focusing on participants with no causal vaccine effect on infection allows isolation of the vaccine's effect on post-infection outcome such as severity of disease: mild, moderate, severe, death.

- Separating these two effects is helpful for designing improved vaccines and for predicting the public health impact of a licensed vaccine.
  - In addition, the PS estimand has a simple interpretation from the perspective of the study participant, addressing his/her question: If I am going to become infected regardless of treatment assignment, will the vaccine reduce the chance of severe disease/death?

Assumptions and Causal vaccine effect

Assumptions:

1) the potential outcomes for each participant are independent of the treatment assignments of other participants,

2) the treatment assignment for each participant is independent of his/her potential outcomes,

3) $\Pr(S(v) = 1, S(p) = 0) = 0$, the vaccine does not increase the risk of acquiring SARS-CoV-2 infection,

4) $Y(p) \perp S(v) \mid S(p) = 1$, among participants who acquired SARS-CoV-2 in the placebo arm, their severe disease or death status, had they been randomized to vaccine, is independent of the observed severe disease or death severity status.

Under these assumptions:

$$\Delta = \pi(v) - \pi(p) = \Pr(Y=1|S=1,Z=1) - \Pr(Y=1|S=1,Z=0)$$

Sensitivity Analysis

- Under assumptions 1) – 3)

$$\pi(v) = \Pr(Y(v) = 1 \mid S(v) = S(p) = 1) = \Pr(Y(v) = 1 \mid S(v) = 1) = \Pr(Y = 1 \mid S = 1, Z = 1)$$

$$\Pr(S(v) = 1 \mid S(p) = 1) = \frac{\Pr(S(v) = 1)}{\Pr(S(p) = 1)} = 1 - VE$$

- Let use a selection model:

$$logit\ P(S(v) = 1 \mid S(p) = 1, Y(p) = y) = \alpha + \beta y$$

- Solve for α:

$$\Pr(S(v) = 1 \mid S(p) = 1) = \sum_{y=0,1} \Pr(S(v) = 1 \mid S(p) = 1, Y(p) = y) \Pr(Y(p) = y \mid S(p) = 1)$$

- For each β, calculate:

$$\pi(p, \beta) = \Pr(Y(p) = 1 \mid S(v) = S(p) = 1) = Pr(S(v) = 1 \mid S(p) = 1, Y(p) = 1) \Pr(Y(p) = 1 \mid S(p) = 1) / (1 - VE)$$

- $\Delta(\beta) = \pi(v) - \pi(p, \beta)$

Conclusions

- The ICH E9(R1) Addendum provides a useful framework for addressing specific objectives of vaccine efficacy studies in a systematic and structured manner.

- Causal vaccine efficacy effects should be clearly defined, and appropriate estimators should be considered.

- Principal stratum strategy for addressing specific intercurrent events in vaccine efficacy trials may be more appropriate than the conventional PP and ITT approaches.

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THANK YOU FOR YOUR ATTENTION

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