Quantification of risk: ask the right questions or time to apply the estimand framework to safety

Basel Biometrics Section Seminar
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Disclosures

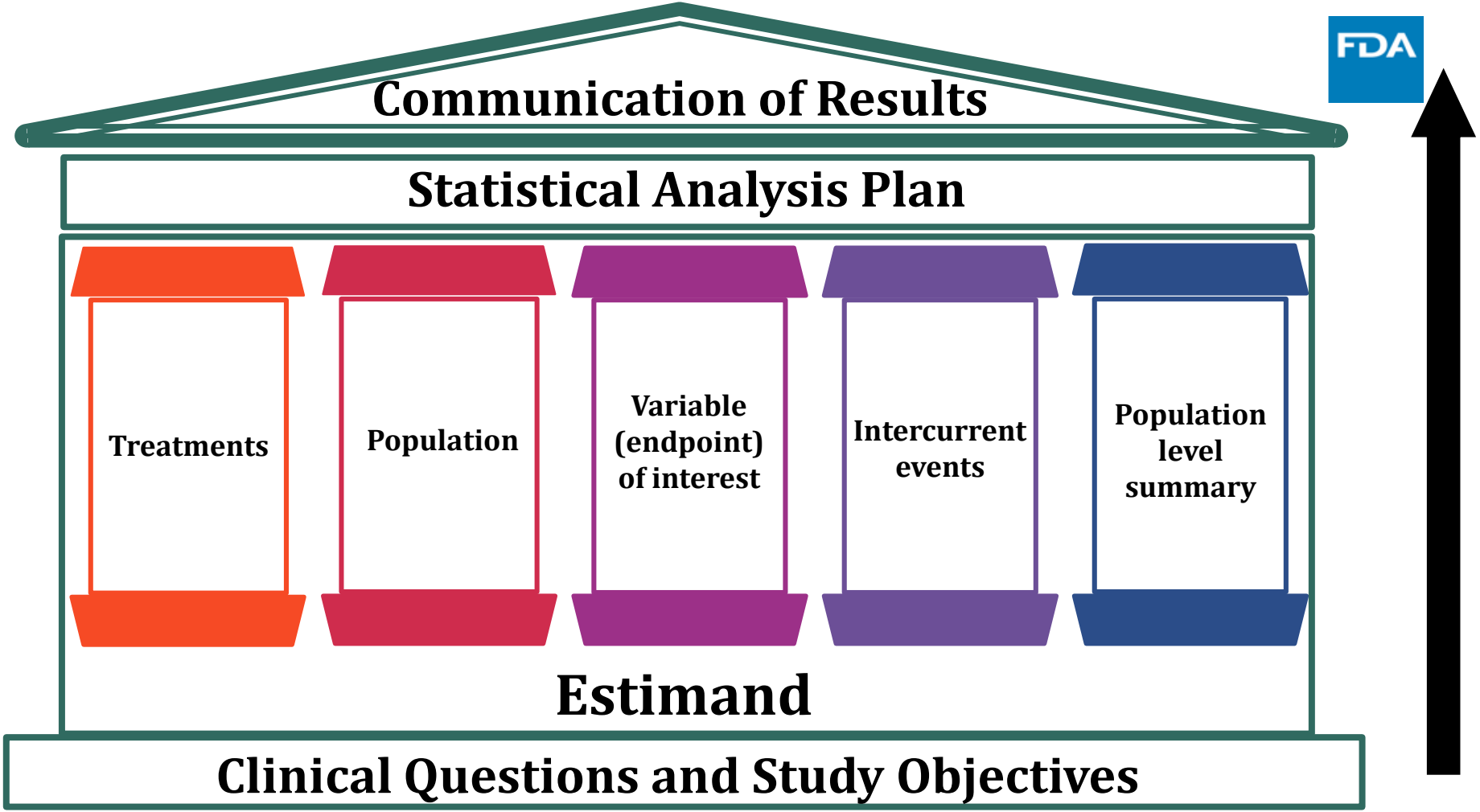
- I have no financial relationships to disclose

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Some Points

- Estimand Framework, Clinical Questions etc.
- On-study, on-treatment etc.
- Competing risk and the Estimand Framework

Estimand Framework, Clinical Questions etc.



Adapted from Fiero, M. H., Pe, M., Weinstock, C., King-Kallimanis, B. L., Komo, S., Klepin, H. D., ... & Sridhara, R. (2020). Demystifying the estimand framework: a case study using patient-reported outcomes in oncology. The Lancet Oncology, 21(10), e488-e494.

Framing the Clinical Question

- **Objective**
- **Population**
- **Endpoint**
- **Treatments**
- **Summary measure**
- **Handling of intercurrent events**

The primary trial objective is <objective, e.g. superiority, non-inferiority or estimation> in <population of interest>.

<Endpoint> will be compared between <test treatment> and <reference treatment> using <summary measure> as a population-level summary, <handling intercurrent events affecting the treatment comparison>.

Adapted from Bell et al. *Pharmaceutical Statistics.* 2021

Example of Clinical Question

- **Objective**
- **Population**
- **Endpoint**
- **Treatments**
- **Summary measure**
- **Handling of intercurrent event**

Is Drug X + SOC non-inferior to placebo + SOC wrt safety in the treatment of adults with type 2 diabetes mellitus?

Hazard ratio for time to first MACE will be compared between Drug X and matching placebo (both treatments in combination with standard of care) regardless (treatment policy) of study treatment discontinuation, initiation of new treatment or change in background medication.

On-study, On-treatment etc.

On-study, On-treatment etc. (1)

- Post randomization events can perturb balance and affect on-study estimands for safety assessments
  - What if logistical errors resulted in all subjects assigned to experimental treatment to receive control and vice versa?
  - In a trial of Experimental treatment + SOC versus Placebo + SOC, what if all subjects on the Experimental treatment arm switched very early in trial (due to mild AEs) to rescue medication that caused SAEs?
  - In a trial of Experimental treatment + SOC versus Placebo + SOC, what if all subjects on the Experimental treatment arm switched very early in trial (due to SAEs) to rescue medication that caused mild AEs?

On-study, On-treatment etc. (2)

- Concerns with on-treatment estimand
  - Distribution of periods under consideration might substantially differ between arms
  - Types of patients who tend to stay on treatment longer might differ between arms
  - Choice of appropriate treatment window can be non-trivial

On-study, On-treatment etc. (3)

- Efficacy and safety assessments required for benefit-risk assessment
- Benefit-risk assessments assisted by “apples-to-apples” comparisons that use the same ICE strategies for efficacy and safety estimands
- Supporting estimands using alternative strategies may be informative for safety evaluations

Competing Risk and the Estimand Framework

Competing Risks and the Estimand Framework

- ICH E9 (R1) estimand framework (EF) is a useful tool that aids cross-disciplinary teams in defining a precise clinical question
- True, ICH E9 (R1) does not mention competing risk (CR)
- This does not prevent incorporating CR into clinical question via other estimand attributes; it does not reduce the utility of the EF
    - EF useful even in cases where you don't "officially" implement it

Example of Clinical Question Incorporating Competing Risk

- **Objective**
- **Population**
- **Endpoint**
- **Treatments**
- **Summary measure**
- **Handling of intercurrent event**

Is Drug X + SOC non-inferior to placebo +SOC wrt safety in the treatment of adults with type 2 diabetes mellitus?

Cause-specific hazard ratio for time to first MACE, accounting for patient deaths before first MACE, will be compared between Drug X and matching placebo (both treatments in combination with standard of care) regardless (treatment policy) of study treatment discontinuation, initiation of new treatment or change in background medication.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