U.S. FOOD & DRUG ADMINISTRATION

Safety Estimands: A Regulatory Perspective

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

OVERVIEW

1 Estimands and the Questions of Clinical Interest

2 Considerations Regarding Safety Estimand Attributes

3 Examples

4 Closing Thoughts

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ESTIMANDS AND THE QUESTIONS OF CLINICAL INTEREST

Estimands

- Estimands for the evaluation of efficacy endpoints becoming more common
- Estimands for the evaluation of safety endpoints not widely used (as of now)

Being Guided by the Science

- April 5, 2017, former FDA Commissioner Scott Gottlieb, M.D. says "**And the American people deserve to trust that the agency is led in an impartial manner -- guided only by the science that informs its work -- and an abiding faith to the public health.**"[1]
- April 15, 2019, acting FDA Commissioner Norman E. "Ned" Sharpless, M.D. says "**First, I believe our efforts should rely on and be guided by the science.**"[2]

[1]https://www.help.senate.gov/imo/media/doc/Gottlieb4.pdf
[2]https://www.fda.gov/news-events/speeches-fda-officials/remarks-acting-commissioner-dr-ned-sharpless-first-all-hands-meeting-04152019

Questions of Clinical Interest

- Answering the wrong questions is bad science
- Therefore, basing regulatory decisions on answers to the wrong questions is bad policy

Example Timeline

Sponsor's analysis plan prespecifies logistic regression with NRI for binary endpoint, and sponsor asks FDA "Do you agree?"

↓

FDA responds "It depends on the estimand you are targeting. Define the estimand."

↓

Sponsor's analysis plan is revised to (w/o clinical justification) define estimand such that:

1. Handling of intercurrent events is that people with missing data are assumed to be nonresponders
2. Population-level summary measure is odds ratio

A Better Timeline

Sponsor's cross-disciplinary team works to determine questions to be addressed by analyses

↓

SAP defines estimands to reflect questions of clinical interest that can be targeted with plausible and (where possible) minimal assumptions

↓

SAP prespecifies analyses that will adequately target estimands

When to Define Estimands

- Estimands should ideally influence not only SAP but also study design and protocol
  - Appropriate study design should be used to reliably evaluate estimands. Therefore, estimands should be defined prior to start of study.
  - Example: If question of clinical interest is regarding comparison to SOC, protocol should not include unnecessary restrictions on background concomitant medications.

“You better think (think) think about what you’re trying to do…”

-Aretha Franklin and Ted White

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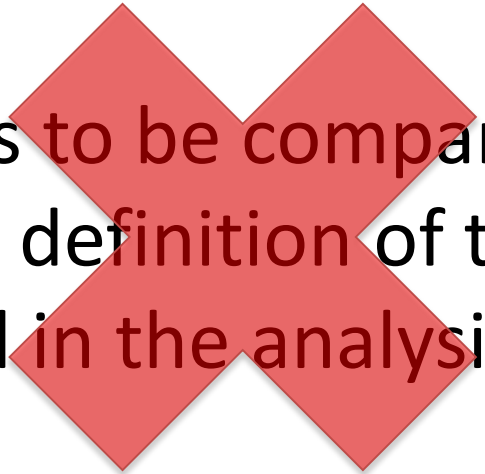
CONSIDERATIONS REGARDING SAFETY ESTIMAND ATTRIBUTES

Safety Estimands

- Same attributes as with efficacy estimands
  - Population
  - Variable (Outcome)
  - How intercurrent events will be handled
  - Population-level summary measure

Population

- The populations to be compared immediately follow from the definition of the safety analysis set prespecified in the analysis plan



- The populations to be compared should reflect the question of clinical interest

Population: Examples

Among patients who meet incl./excl. criteria:

Those who are randomized to the highest dose of investigational product
vs.
Those who are randomized to the reference product

Those who receive at least one dose (at any level) of the investigational product
vs.
Those who receive at least one dose of the reference product

Those who are exposed to the investigational product for at least 7 days
vs.
Those who are exposed to the reference product for at least 7 days

Variable (Outcome)

- Common choice: Binary indicator of whether AE occurred at least once
- Other outcomes of clinical interest may consider
  - Time to first instance of AE
  - Severity of AE
  - Duration of AE
  - Any recurring events of AE

How Intercurrent Events Will be Handled

- Should be informed by cross-disciplinary discussion
- Two well-known approaches: “treatment policy” and “while on treatment”

Treatment Policy Approach

- An attempt to compare treatment policies
  - That is, to compare risk of outcome in patients in experimental treatment population versus that in those in control treatment population, regardless of treatment adherence, treatment discontinuation, or use of alternative therapies
- Use facilitated by study protocol's implementation of efforts to retain patients in study for regularly scheduled assessments even after they discontinue, change, or fail to adhere to assigned treatment

Treatment Policy Approach

- May be important if control arm receives a reasonable representation of current standard of care
  - This approach can help assess what may happen to target population if investigational product is approved for marketing
- May provide greater sensitivity to adverse effects on outcomes with potentially long latency periods, such as malignancy
- May be relevant in cases where pre-cursor event that results in treatment discontinuation occurs prior to observing AE

While on Treatment Approach

- Restricts data being used to those collected while patient was receiving assigned treatment, plus perhaps those collected a certain amount of time after treatment discontinuation
- May be important if one question of clinical interest is whether taking investigational product adversely affects patients in targeted population while they are taking the product

While on Treatment Approach

- May provide greater sensitivity if investigational product only or primarily increases risk while patients are taking it (i.e., any increases in risk go away after treatment discontinuation), such as anaphylaxis
  - Assumes that events occurring off-treatment are independent of the reason for discontinuing treatment
- There may be issues of interpretability if there are systematic between-arm differences in types of patients who remain on treatment or in how long patients remain on treatment

How Intercurrent Events Will be Handled

- Choice of approach(es) will likely depend on
  - Variable/Outcome
  - Context of investigational product's development program (including benefit-risk profiles of products currently marketed for targeted population along with what is known about disease mechanism and drug class)
- It may often be of interest to evaluate both treatment policy and while on treatment estimands, because each approach may offer certain insights

Summary Measure: General Strategy

- Step 1: Define “within-arm” summary measure
- Step 2: Use “within-arm” summary measure to define “between-arm” summary measure

Summary Measure

- If primary clinical interest is in whether AE occurred at least once, we may consider
  - Cumulative incidence (incidence proportion): probability that AE occurred at least once *before given time point*
    - "Between-arm" summary measures include risk difference, relative risk, and odds ratio
  - Incidence rate: number of instances of AE occurring at least once per population at risk in given time period
    - "Between-arm" summary measures include difference in incidence rates

Summary Measure

- If primary clinical interest is in how often AE occurred while taking into account recurrent instances of AE, we may consider
  - Rate: number of AE occurrences per population at risk in given time period
    - "Between-arm" summary measures include difference in rates

Summary Measure

- If primary clinical interest is in time until first instance of AE, we may consider
  - Hazard rate*
    - "Between-arm" summary measures include hazard ratio
  - Survival function*
    - "Between-arm" summary measures include acceleration factor (scaling factor): variable A in $S_{IP}(t) = S_{RP}(At)$

*Completely defines (rather than summarizes) the distribution

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EXAMPLES

Decisions Made During NDA/BLA Review

- Given the benefits of the investigational product and the context under which the product is being developed (including the nature of the disease and the availability of other products in the market), is the safety profile for the investigational product sufficiently favorable in the US disease population under consideration such that the Agency should approve the product?
- If the investigational product is approved, what safety information should be included in labeling to properly inform patients and prescribers?

Example 1

- Question of clinical interest (Approval): What would be the effect (with respect to the cumulative incidence of having at least one anaphylactic reaction in the first 52 weeks) of being prescribed the highest dose level of the investigational product, compared to being prescribed what is currently standard of care treatment?
  - Goal: Estimate the effect (with respect to anaphylactic reactions) on the US disease population under consideration of approving the investigational product
- Candidate Estimand
  - Population: Among patients who meet inclusion/exclusion criteria, those who receive any of the highest dose level of the investigational product, compared to those who receive at least one dose of standard of care treatment
  - Variable (Outcome): Binary indicator of having at least once instance of anaphylactic reactions
  - How intercurrents will be handled: treatment discontinuation, lack of treatment adherence, and use of alternative therapies will be ignored
  - Summary measure: Difference in cumulative incidence through Week 52, between the two populations being compared

Example 2

- Question of clinical interest (Labeling + Approval): What is the effect (with respect to the incidence rate of having at least one anaphylactic reaction before Week 52) of taking the investigational product at any dose level, compared to taking placebo?
  - Goal: Estimate the effect (with respect to anaphylactic reactions) of a patient in the US disease population under consideration taking the investigational product
- Candidate Estimand
  - Population: Among patients who meet inclusion/exclusion criteria, those who receive any amount of the investigational product, compared to those who receive at least one dose of placebo
  - Variable (Outcome): Binary indicator of having at least once instance of anaphylactic reactions
  - How intercurrents will be handled: Data collected beyond 7 days after permanent switch to the use of alternative therapies or permanent treatment discontinuation will be excluded
  - Summary measure: Difference in incidence rates through Week 52 between the two populations being compared

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CLOSING THOUGHTS

Key Takeaways

- Good science requires that we seek answers to right questions
- When defining estimands, collaboration with clinical colleagues is critical to ensure that questions of clinical interest are being addressed
- Questions of clinical interest should influence estimands to be targeted, which in turn should influence (1) study design and protocol and (2) analyses to be performed


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