Deriving Estimands for Pulmonology-Allergy Indications in US FDA Regulatory Submissions

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Abstract

In regulatory interactions between the Agency and sponsors for new drug development, agreement on estimands is critical because framing the clinical question with the estimand has direct impact on clinical trial design and conduct and ultimately drug approval and labeling claims. In 2019, ICH published an addendum to E9 Statistical Principles for Clinical Trials which provides guidance on estimands in clinical trials. The addendum provides general principles and framework on estimands. Interpretation of the general principles requires Agency guidance to tailor the principles to specific indications and development programs. This presentation showcases a collaborative effort to derive clinically relevant and statistically sound estimands for clinical trials in common pulmonology-allergy disease areas.

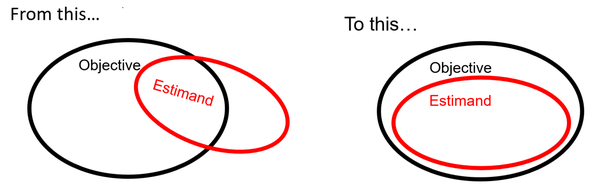
Introduction

- 1998: Statistical principles for clinical trials delineated in the ICH E9 guidance published
  - Emphasized ITT principles and the associated treatment policy effect as a target of estimation
- 2010: National Academy of Science report titled 'Prevention and Treatment of Missing Data in Clinical Trials' with major recommendations
  - Distinguished 'analysis dropout' from 'study dropout' and continued to collect efficacy and safety data even after discontinuation of treatment to minimize missing data
  - Defined an estimand aligned with the trial objective in the protocol
- 2019: Addendum to ICH E9 guidance (draft available 2017)
  - Clarified estimands with introduction of 'intercurrent events' as essential component
  - Provided example strategies to account for such events
  - Envisioned different strategies to address various intercurrent events other than treatment policy strategy strongly advocated in ICH E9 guidance
  - Finalized in 2019 to be implemented in phase 3 protocols and statistical analysis plans (SAPs)

Materials and Methods

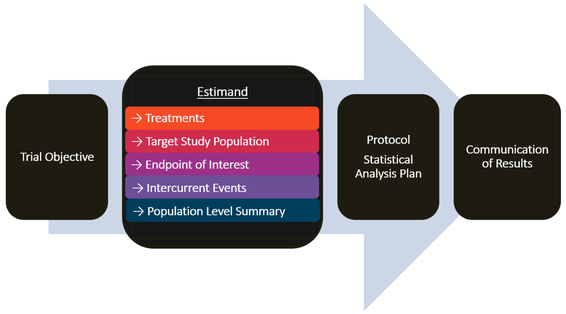
If an estimand does not reflect the clinical question of interest, statistical methods to estimate the treatment effect would reflect such limitation and often lead to unintended biased conclusion. Statistics needs a clear target for estimation. The statistical analysis will not correct a wrong target.

Figure 1. Aligning Trial Objective with Estimand



Estimands as precisely defined treatment effects determine trial design and statistical methods. Considerations of the impact on study design elements and statistical methods need to be evaluated for each estimand.

Figure 2. Estimand Roadmap



- Although not specifically defined in the protocols, historically estimands were characterized with elements of population, treatment descriptions/ conditions, endpoints, and summary measures to be compared in the analysis.
- Intercurrent events were not systematically defined and often conflated with missing data.
- Now, the Agency asks trial sponsors to
  - prespecify intercurrent events and how they are handled in the analysis
  - distinguish intercurrent events from missing data

Estimands in Pulmonology and Allergy

- IND input to sponsors about estimands can have a direct impact on both drug approval and labeling claims
- Prespecified estimands to improve clarity, especially for handling of intercurrent events and their effect on clinical interpretation
- Acknowledge the need for clinical input (collaboration)
- Knowing what data to include might be disease-specific or affected by clinical practice
- Goal: Derive clinically meaningful and statistically appropriate estimands to discuss with the sponsor more effectively and efficiently
- Progress: Ongoing efforts by DPACC and pulmonary statisticians to use estimand framework in confirmatory trial protocols and SAPs
- Create 'default' estimands for most active disease areas

Results and Discussion

A. A section with estimand considerations is appropriate in future clinical guidance documents for trial sponsors.

As a case example, previously utilized estimands from approved NDA/BLAs for chronic rhinosinusitis with nasal polyposis (CRSwNP) are discussed and incorporated in estimand feedback in subsequent INDs and NDA/BLAs.

As a coprimary endpoint, nasal polyp score (NPS, values from 0-8) is collected for 6 months treatment duration. The summary measure is change from baseline at 6 months compared between treatments. A major intercurrent event is nasal polyp surgery, which makes data after surgery clinically meaningless. Surgery warrants a replacement value to indicate treatment failure. For the value, the clinical and statistical team considered some simulated but plausible patient journeys (Figure 3.a). These cases clarified the clinicians' decision that the worst possible score (8) is the most appropriate replacement value to reflect treatment failure experienced by patients resorting to surgery (Figure 3.b).

Figure 3.a. CRSwNP Patient Journey, Initial Data and Clinician's Ranking

NPS	Months							Rank
Case	0	1	2	3	4	5	6	
A	6	6	5	5	6	6	6	2
B	6	6	5	5	6	surg 0	0	3
C	3	2	3	3	7	4	3	1
D	3	2	3	3	7	surg 0	0	4

- Team created patient journeys for cases to better understand consequences of this intercurrent event
- NPS scores ranged from 0-8
- Worst observed score in the journey noted in red
- Clinicians were asked to rank outcomes
- Rank 1 reflects the best clinical outcome and Rank 4 reflects the worst clinical outcome
- Team discussed implications related to estimand strategy

Figure 3.b. CRSwNP Patient Journey with Values Used in Analysis

NPS	Months							Rank	VIA
Case	0	1	2	3	4	5	6		
A	6	6	5	5	6	6	6	2	6
B	6	6	5	5	6	surg 0	0	3	8
C	3	2	3	3	7	4	3	1	3
D	3	2	3	3	7	surg 0	0	4	8

- Score of 8 assigned for NP Surgery
- Value in Analysis (VIA): value at Month 6
- Realizing that cases with surgery and without ranked differently was helpful
- The previous "worst observed score" approach didn't differentiate between cases A and B, but the "value in analysis" aligned the ordering of these cases with the clinical evaluation

B. Most IND reviews of phase 3 protocols and statistical analysis plans (SAPs) in Division of Pulmonology, Allergy and Critical Care now include estimands and estimators.

- Better/clear understanding of estimands
  - Clear alignment between clinical question and analysis
  - Consistency across sponsors for indications
  - Estimand framework is making CRSwNP NDAs/BLAs of better quality
  - 5 estimand attributes cover the important bases for design, conduct, analysis
  - Makes it easier to communicate mis-alignments within FDA review team and with sponsor
- CDER Estimands Wiki
  - IND and NDA/BLA review comments on estimands were summarized on the Wiki so that prior precedents are easy to find
  - Clinical insights and revisions where needed have been added on the Wiki
  - Clinically/Statistically agreed IND input has been sent to some sponsors based on what we agreed on the Wiki for particular indications

Conclusion

The estimand framework is designed to align the trial design and statistical methods to the clinical trial objective. Through making recommendations on the attributes of this framework on study design, data collection, statistical methods and subsequent interpretation, the FDA provides valuable IND feedback to sponsors for offering better alignment between study goals, analysis and interpretation in NDAs and BLAs.

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