Paper AS10

Vision to Decision: An Ocular case study on Estimand

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ABSTRACT

Estimand framework in clinical trials is a systematic approach to defining the treatment effect of interest, ensuring clarity in study design, analysis, and interpretation. It addresses potential intercurrent events (ICEs), which are occurrences during a trial that affect the interpretation of the treatment effect, like discontinuations or rescue medication.

From a programming perspective, implementing estimand requires a systematic and reliable approach. It begins with mapping estimand definitions to data structures, leveraging standards like CDISC SDTM and ADaM. ADaM datasets are particularly crucial as they support estimand-aligned analyses by incorporating derived variables and flags that reflect intercurrent events.

In this case study of eye related issues, we discuss the examples of primary, supplementary eye endpoints and corresponding estimand, defined intercurrent events, sensitivity analysis of these endpoints and how we approached it programmatically.

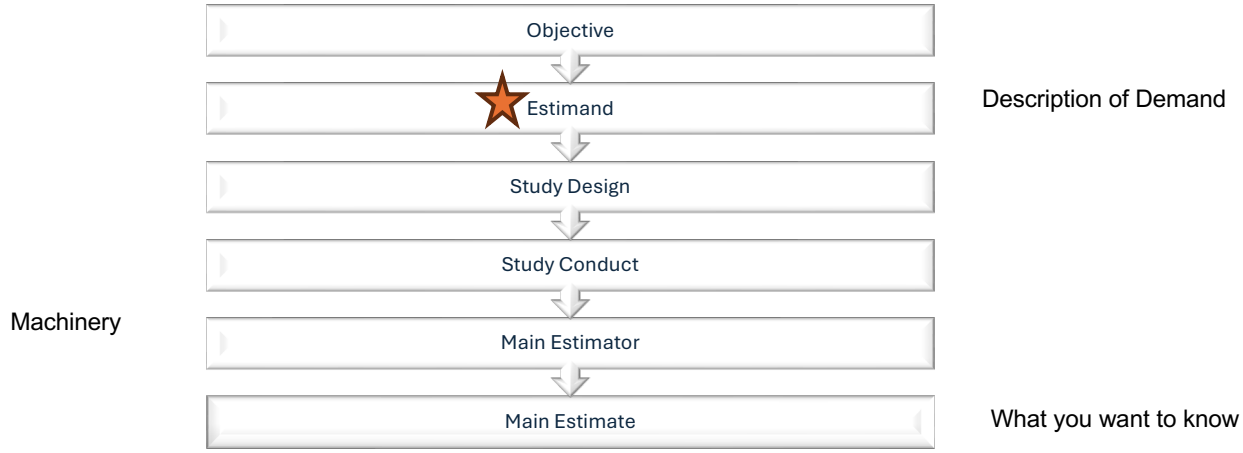
INTRODUCTION

The estimand framework provides a structured approach to precisely define the treatment effect of interest in clinical trials, ensuring alignment between study objectives, design, analysis, and interpretation.

Its implementation clarifies how intercurrent events are addressed by explicitly specifying the target population, endpoint, handling strategy, and summary measure.

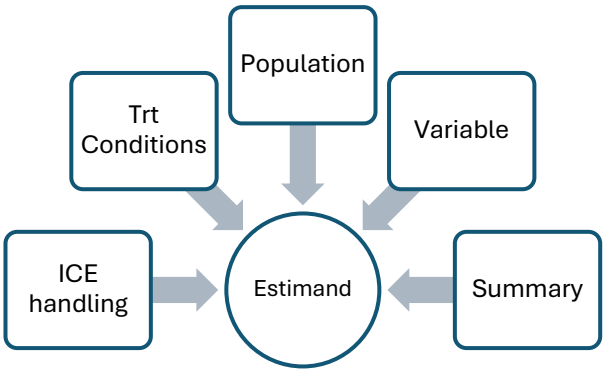
ICH E9 estimand framework addresses key ambiguities

- Recognizes that treatment effects of interest are often not explicitly or precisely defined at the outset of a clinical trial.
- Limited transparency regarding how intercurrent events are addressed in the definition of the treatment effect.
- Traditional trial practice in which data collection and analysis methods implicitly determine the treatment effect being estimated.
- A shift towards explicitly defining the estimand of interest first, such that it directly informs and guides the data collection strategy and analytical approach.



Attributes

Below are the main attributes of estimand. ICEs can be incorporated in treatment, population and/or variable attributes.



Intercurrent Event:

"Events that occur after treatment initiation and either preclude observation of the variable or affect its interpretation" e.g.: Rescue medication, Treatment discontinuation.

There is different ICE handling mentioned in the ICH E9 guidelines:

- Treatment Policy- Targets the treatment effect **regardless of/despite** the occurrence of intercurrent event (Intercurrent event considered as part of the treatment).
- Hypothetical- A hypothetical scenario is envisaged in which the ICE would not occur.
- Composite- The occurrence of the intercurrent event is included in the outcome variable by assigning it to a particular value of the outcome variable.

In ophthalmic clinical trials too, implementation of the estimand framework is critical for clearly defining treatment effects in the presence of disease-specific intercurrent events such as treatment discontinuation, rescue therapy, fellow-eye involvement, or surgical interventions.

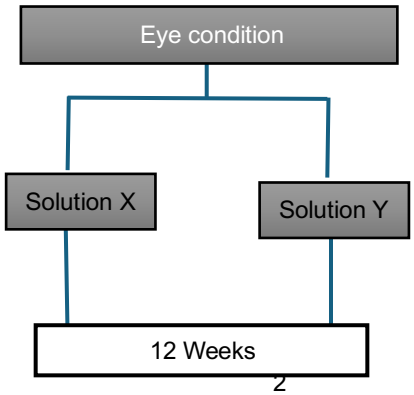
By explicitly specifying how events like rescue medication, emergency medications, or use of adjunctive therapies are handled, the estimand framework ensures alignment between clinical objectives, trial design, and analysis.

Its implementation enhances transparency and interpretability of endpoints such as visual acuity, intraocular pressure, or retinal thickness, supporting clinically meaningful conclusions and regulatory decision-making in ophthalmology.

A case study describes how concepts get utilized for an Ocular test study, where we explain the concept usage in primary estimand and secondary estimand. Finally, derivation of ADICE and ADEFF is achieved which get utilized for ICE handling strategies.

Overview of Study

Objective:
To compare a12-week course of a new Solution X against marketed Solution Y in routine practice for subjects having eye related issues.



- Usage of medication is available that may be emergency medication stated and may or may not affect the treatment effect.
- What do we want to find out: Difference in Solution X and Solution Y at end of week 12. Is this objective ambiguous? We know the usage of emergency medication will affect the results. Early discontinuation due to Adverse events will also disrupt the interpretation.

Estimand description: Use of emergency medication.

Handling Intercurrent events:

- Ideal: Use of emergency medication is not necessary.
- Treatment Policy: use of emergency medication is ignored and considered as treatment.
- Hypothetical: No emergency medication has been taken.

Treatment:

- Ideal: Experimental: Solution X, Control: Solution Y.
- Treatment policy: Solution X +emergency medication, Solution Y + emergency medication.
- Hypothetical: Experimental: Solution X, Control: Solution Y.

Population: As defined by Inclusion/Exclusion Criteria.

Variable: Change in Eye Condition from baseline to week 12.

Population level difference: Mean difference.

Individual attributes of the estimand change when the various strategies are used for the ICE use of emergency medication.

Impact of estimand:

- Trial design follows the specification of estimand.
- Trial conduct w.r.t. type, duration, discontinuation criteria, medication to be used or not, measurement of efficacy parameters.
- Data collection: Collect data post treatment discontinuation as per treatment policy.

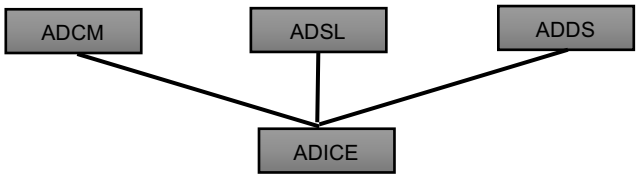
Derivation of ADICE, ADEFF

ADICE Derivation

Each record represents one ICE event with its timing and assigned strategy. Based on the intercurrent events defined in the definition of handling of intercurrent events EST01STP holds strategy associated with ICE and EST01STA holds the actual strategy.

As per handling of ICE the data required is particularly from 3 datasets which are needed to create ADICE dataset.

1. ADCM: Emergency medication is flagged in ADCM for each subject which is also ICE of interest.
2. ADDS: The reason for discontinuation collected in disposition dataset becomes the source for ADICE too.
3. ADSL: Subjects who got NOTASSIGNED to any treatment for any reason and have no post randomization data are ICE of interest.



Analysis	ATERM	ADECOD1	ASTDT	AENDT	EST01STP	EST02STP	EST03STP
1	AZITHROMYCIN	Use of emergency medication not expected to influence eye	23-Jul-21	23-Jul-21			
2	AZITHROMYCIN	Use of emergency medication not expected to influence eye	23-Jul-21	23-Jul-21	Treatment Policy	Treatment Policy	Treatment Policy

Note: A subject might have more than one ICE event. The strategy in ADEFF will be based on ICE event with higher priority.

ADEFF Derivation

The efficacy data derived based on the variable which is of importance in this study. In the above example, the variable which is IOP- intra ocular pressure.

The data from eye related issue dataset used to merge with ADICE to get required EST01STP, EST01STA and corresponding ICE start /End date.

Example: Derivation logic for EST01STP

To set the value of ADICE.EST01STP follow the below steps:

- Populate the strategy for the records where ADEFF.adt>=ADICE.astdt.
- For Emergency medication ICEs, where ICE end date is not missing then populate values based on ADICE.AENDT. Ensure ADEFF.ADT is in between ADICE.ASTDT and ADICE.AENDT.
- If an emergency medication has no end date, then flag for all visits after starting date.
- If a subject has missing data and it is not impacted by ICE and end of study status is completed or discontinued, then assign "Hypothetical "

Other estimand derivations are done in ADEFF as per above logic. After the derivation of these datapoint for each subject with impacted ICE strategies, we must derive impact flags for ICE events per estimand.
E.g.: ICE01S, ICEO2S. These document data point affected by intercurrent events.

	A	B	C	D	E	F	G	H	I
1	SUBJID	ASTDT	AENDT	ADT	ADECOD1	EST01STP	EST01STP	ICE01S	
2	XX1			13-May-2021					
3	XX1			14-May-2021					
4	XX1			15-May-2021					
5	XX1			16-May-2021					
6	XX1			17-May-2021					
7	XX1			18-May-2021					
8	XX1	19-May-2021		19-May-2021	Emergency Medication taken	Treatment Policy	Treatment Policy	1	

CONCLUSION

This paper outlines how the estimand framework is transforming the design and conduct of clinical trials. It also presents a use case from an ocular study illustrating key estimand attributes along with implementation of ADICE and ADEFF.

REFERENCES

1. ICH harmonized guideline addendum on estimand and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials E9(R1). ICH Consensus Guideline. 2021. Revision 1.

2. Appendix examples

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