

# Single Day Event

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## The implementation of the estimand framework: from concepts to outputs in a case study



# Why “Estimand”?

Question: Patient A took a rescue medication before primary endpoint assessments (week 16). Data afterwards were collected. How to evaluate the treatment effect data at week 16 of patient A?

*Option 1:* Regard the event of taking rescue medication as “Non-responder”.

*Option 2:* Ignore the fact that the patient took a rescue medication, use the data collected directly.

*Option 3:* Remove data collected after taking rescue medication and use multiple imputation to impute.



# Why “Estimand”?

*The answer depends on the **study objective**.*

Option 1: Regard the event as “**Non-responder**”:

“consider using rescue medication as an unfavorable outcome”

Option 2: **Ignore** the event :

”what is the treatment effect (incl. possible taking rescue medication) vs placebo (incl. possible taking rescue medication) before week 16?”

Option 3: **Use multiple imputation** to impute data after the event :

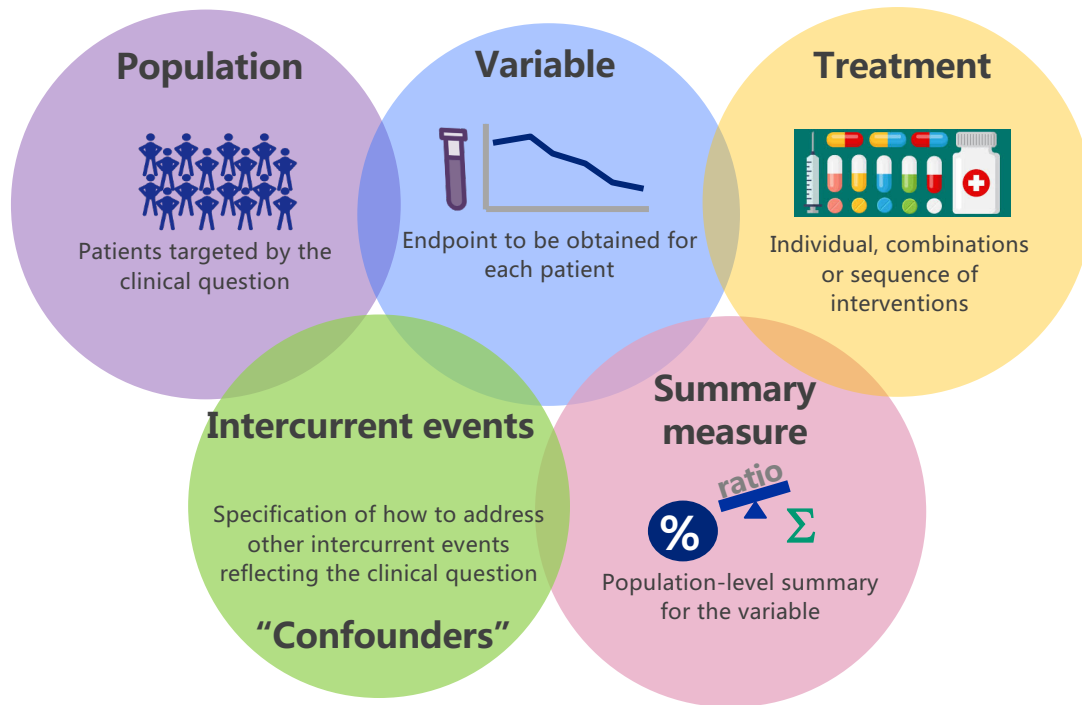
”... if the event of taking rescue medication would not have happened?”

# What is an “Estimand”?

## *ICH E9 Addendum*

- A structured framework that **translate** the **trial objective** into a **precise definition** of the treatment effect that is to be estimated
- It aims to facilitate the dialogue between disciplines involved in clinical trial planning, conduct, analysis and interpretation, as well as between sponsor and regulator, regarding the treatment effects of interest that a clinical trial should address

# Description of an estimand





# Strategy to address Intercurrent Events

Option 1: Regard the event as “Non-responder”:

“consider using rescue medication as an unfavorable outcome”

Composite strategy

Option 2: Ignore the event :

”what is the treatment effect (incl. possible taking rescue medication) vs placebo (incl. possible taking rescue medication) before week 16?”

Treatment Policy strategy

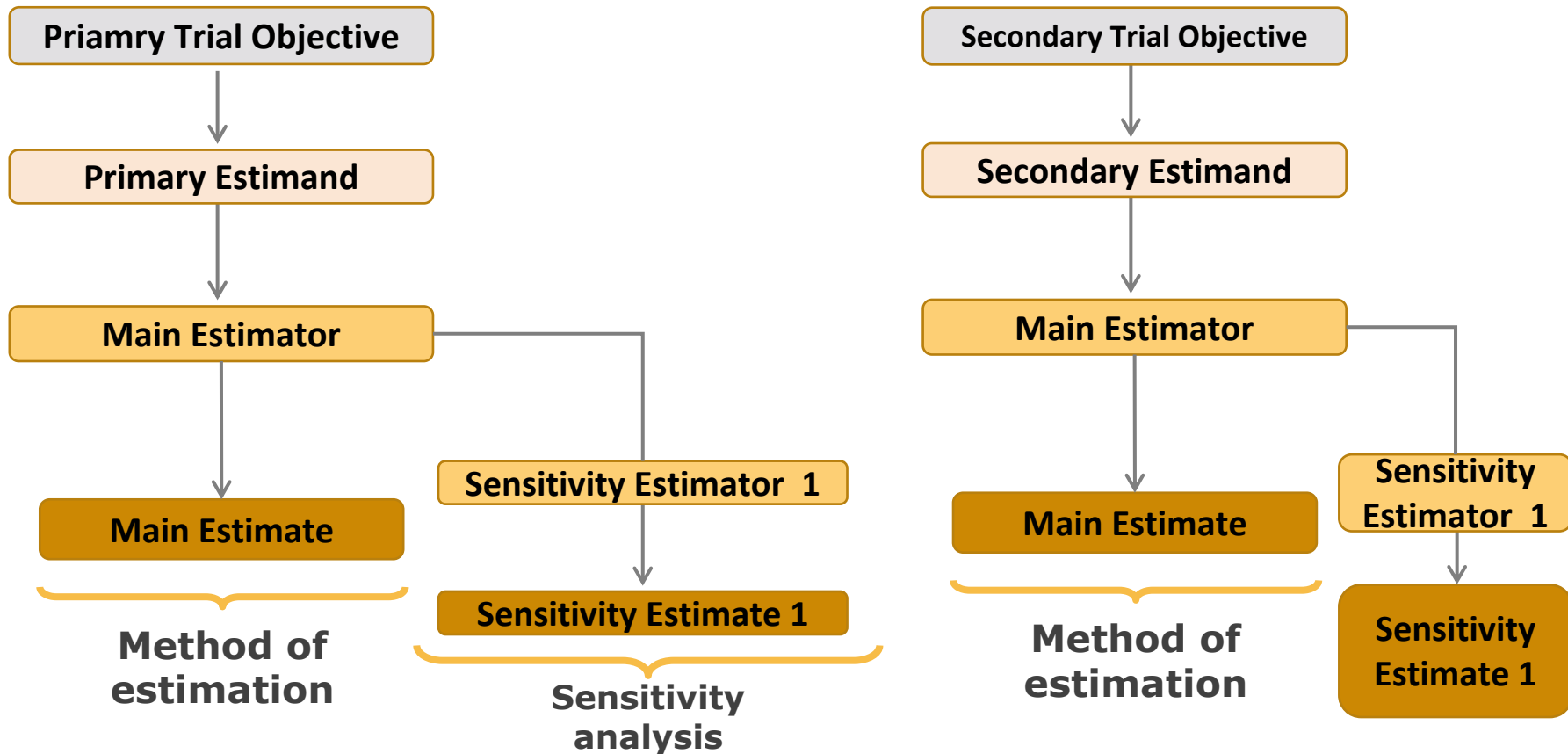
Option 3: Use multiple imputation to impute data after the event :

”... if the event of taking rescue medication would not have happened?”

Hypothetical strategy



# Trial objective and estimand



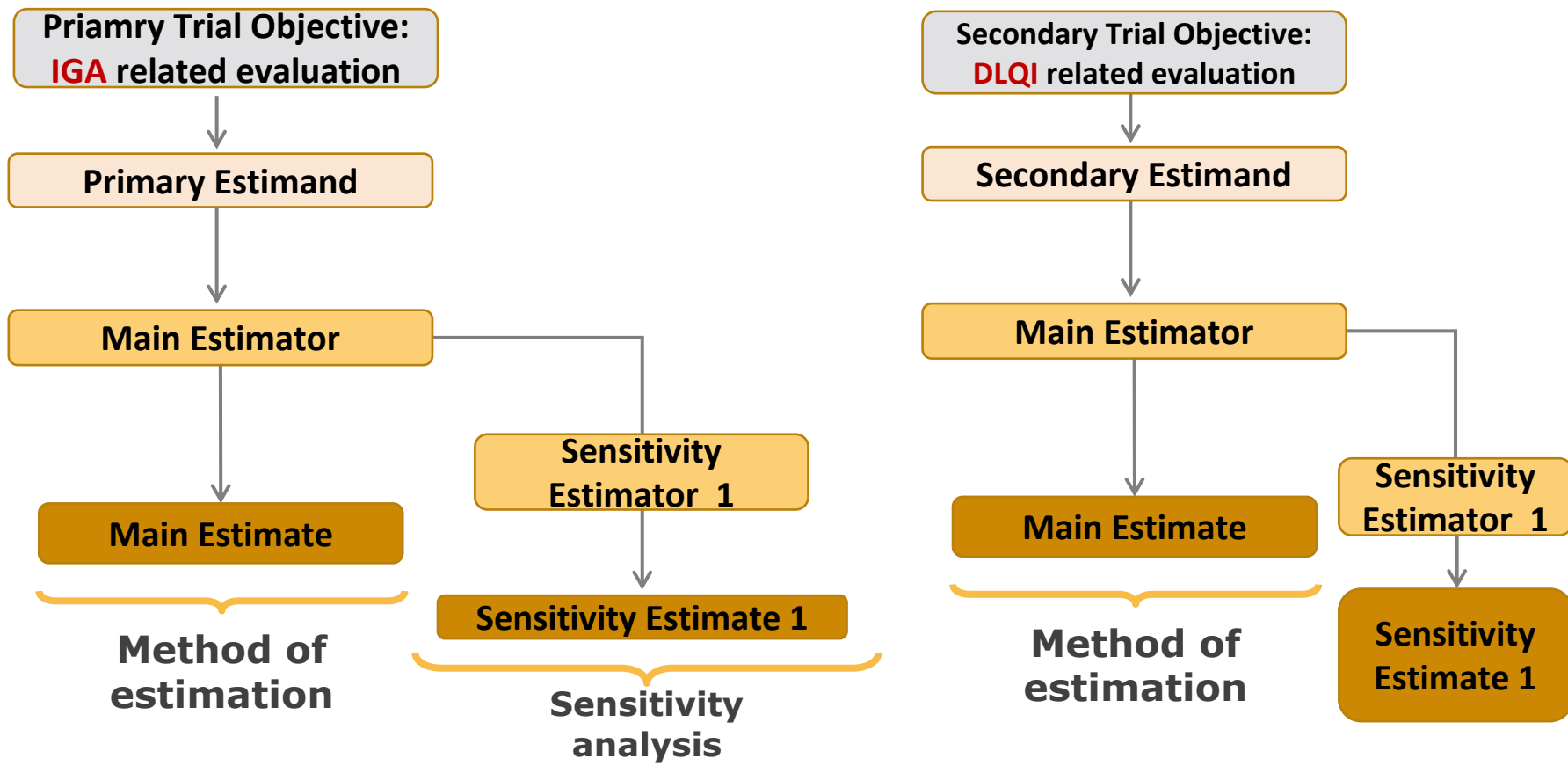


# A case study: a Ph2a PoC study

- **Population:** Patients with disease A who are naïve to biologic therapy and are intolerant or having inadequate response to conventional treatment
- **Variable:** Composite variable of IGA response 0/1 at week 16 and treatment discontinuation due to any reason: For patients without treatment discontinuation, the actual IGA response 0/1 at week 16 is used; for patients that discontinued treatment, "non-responder" is assigned.
- **Treatment:** Drug X vs Placebo
- **Intercurrent events:**
  - Treatment discontinuation due to any reason → **composite strategy** (discontinuation of treatment is a "treatment failure")
- **Summary measure:** posterior distribution of treatment effect difference between Drug X and placebo.



# Primary and secondary estimands





# Impact on trial design, conduct and analysis

## Design

Cross-functional discussion to define trial objectives using estimands  
Protocols/SAP to reflect estimand framework



## Conduct

- CRF designing: disposition page, EOT/ EOS assessments
- Data collection after intercurrent events



## Analysis

- ADaM dataset preparation tailored to estimands
- Use of Flags for different estimands



# Special considerations in practice

## -- Data collection

- Protocol language for data collection

- e.g. “Subjects who discontinue study treatment will continue to be followed up for as long as possible, and efforts should be made so that subjects continue study visits as per the assessment schedule even if not on study drug.”

- CRF page design

To capture the time and assessments after treatment discontinuation, we may need:

- additional disposition page for [period/study](#)
- additional visit pages for [period/study](#)



# Special considerations in practice

## -- Data preparation

- ADaM preparation:

- Flags for assessment “imputed” and used under different estimand framework

| SUBJID | VISIT | PARAM  | AVAL | Derived | Flag_estimand1<br>(Composite) | Flag_estimand2<br>(Hypothetical) |
|--------|-------|--------|------|---------|-------------------------------|----------------------------------|
| 1      | 8     | IGA0/1 | 1    | N       | .                             | .                                |
| 1      | 9     | IGA0/1 | 0    | N       | .                             | .                                |
| 1      | 8     | IGA0/1 | 0    | Y       | Y                             | .                                |
| 1      | 9     | IGA0/1 | 0    | Y       | Y                             | .                                |
| 1      | 8     | IGA0/1 | 1    | Y       | .                             | Y                                |
| 1      | 9     | IGA0/1 | 1    | Y       | .                             | Y                                |

- Hierarchies when multiple intercurrent applies.

# Special considerations in practice

## -- outputs (1)

**Table. Disposition**

| Disposition/Reason                        | Drug X<br>N=xxx<br>n (%) | Placebo<br>N=xxx<br>n (%) |
|-------------------------------------------|--------------------------|---------------------------|
| Completed treatment period 1              | xx (xx.x)                | xx (xx.x)                 |
| Discontinued treatment                    | xx (xx.x)                | xx (xx.x)                 |
| Primary reason for discontinued Treatment |                          |                           |
| Adverse event                             | xx (xx.x)                | xx (xx.x)                 |
| Death                                     | xx (xx.x)                | xx (xx.x)                 |
| ...                                       |                          |                           |
| Discontinued Study                        | xx (xx.x)                | xx (xx.x)                 |
| Primary reason for discontinued Study     |                          |                           |
| Adverse event                             | xx (xx.x)                | xx (xx.x)                 |
| Death                                     | xx (xx.x)                | xx (xx.x)                 |



# Special considerations in practice

## -- outputs (2)

**Table. Number of intercurrent events up to Week 16 (primary estimand)**

| Intercurrent event                              | Drug X<br>N=xx |         | Placebo<br>N=xx |         |
|-------------------------------------------------|----------------|---------|-----------------|---------|
|                                                 | n/m            | (%)     | n/m             | (%)     |
| 1. Intake of prohibited medication/treatment    | xxx/xxx        | (xxx.x) | xxx/xxx         | (xxx.x) |
| 2. Intake of rescue medication                  | xxx/xxx        | (xxx.x) | xxx/xxx         | (xxx.x) |
| 3. Permanent discontinuation of study treatment | xxx/xxx        | (xxx.x) | xxx/xxx         | (xxx.x) |

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# Thanks for listening

## Q & A



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