Can the Estimand Framework help improve the analysis of adverse events of special interest?

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CONTRIBUTED **SESSION:** *Estimands for time-to-event outcomes: re-thinking old questions within the Estimand framework*

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Content

- Analysis of Adverse Events of Special Interest (AESI)
- Case Study
- Strategies to handle ICEs and define treatment effects
  - Similarities and differences between Efficacy and Safety
- Summary and Conclusions

Adverse Events of Special Interest (AESI)

- When an Investigational Product reaches Phase III, we often have an idea about the **safety profile** of the drug based on prior evidence:
  - AEs identified in preclinical development, Phase I, Phase II
  - AEs of drugs with same mechanism of action (class effects)
  - Example: *Immunomodulators increase the risk of infections*

- **AESI** are AEs of medical concern, **possibly affected by the drug**, that require further investigation
- Safety Analyses to **characterize AESI** is an important aspect in clinical development
- The **Estimand Framework** can be used to define **precise treatment effects** for AESI

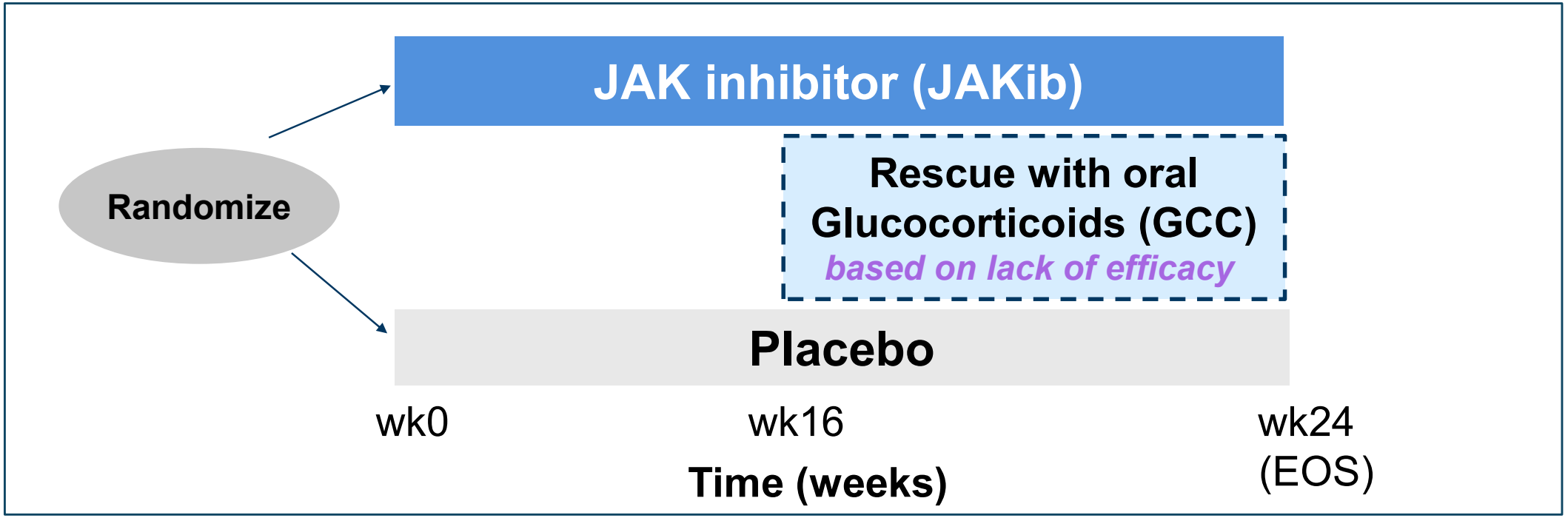
Estimand attributes

Treatment	Treatments or treatment regimens to be compared, describing how they are administered and for how long
Population	Target population for which the treatment effect is being estimated
Variable	Outcome measure needed to address the question of interest
Population-level Summary Measure	Estimate used to compare the outcomes between the different treatments *(e.g. risk ratio, difference in proportions, difference in means)*
Strategy to handle Intercurrent Events (ICE)	How **ICEs** (*e.g., treatment discontinuations, rescue medication)* are used to **specify treatment effects of interest** *(i.e., how to define precise scientific questions)*

Synthetic Case Study: Design

Phase III RCT in Rheumatoid Arthritis (RA)

Study Design



RA Case Study: Endpoints

- **Efficacy**: based on the **Clinical Disease Activity Index (CDAI)**
  - ***Remission; Low Disease Activity (LDA)***
  - ***Moderate Disease Activity (MDA); High Disease Activity (HDA)***
- **AESI**: known safety risks related to the **use of JAKibs**
  - Risk of Respiratory Tract Infection (RTI)
  - Hypercholesterolemia (increase of LDL-cholesterol)

Efficacy endpoints

Primary Endpoint: Achieving Remission (CDAI ≤ 2.8) at wk 24

Secondary Endpoint: Change from baseline in VAS-PAIN at wk24

Safety endpoints

AESIs:

- Experiencing at least one RTI during the 24 weeks of study
- Change from baseline in LDL-c at wk 24

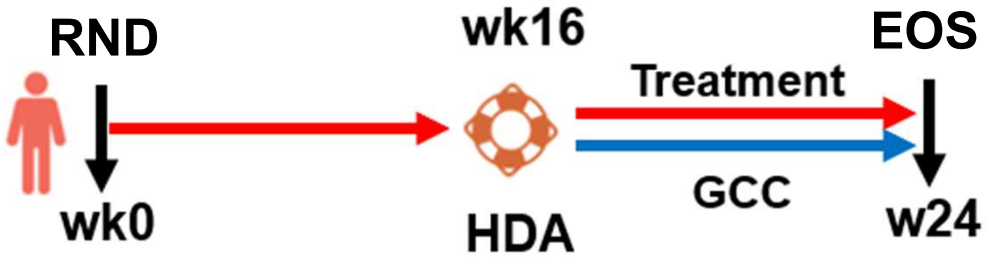
RA Case Study: Intercurrent Events (ICE)

Rescue: **Oral Glucocorticoids (GCC)** starting at any time at or after w16 if **response to treatment as defined in protocol** is not adequate (e.g., patients in **HDA**)

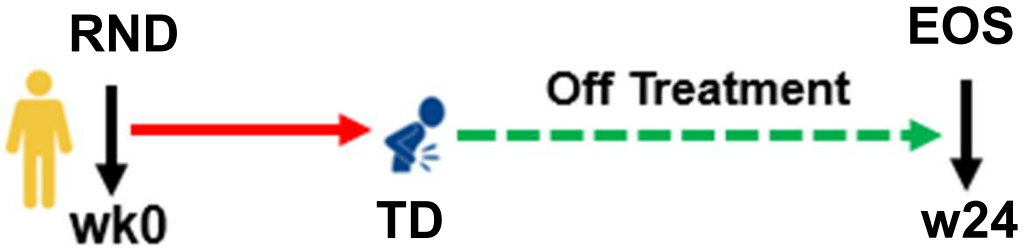
Known Safety issues related to the **use of oral GCC**

- Risk of infection
- Hypercholesterolemia (increase of LDL-cholesterol)

***Rescue**: GCCs because inadequate response*

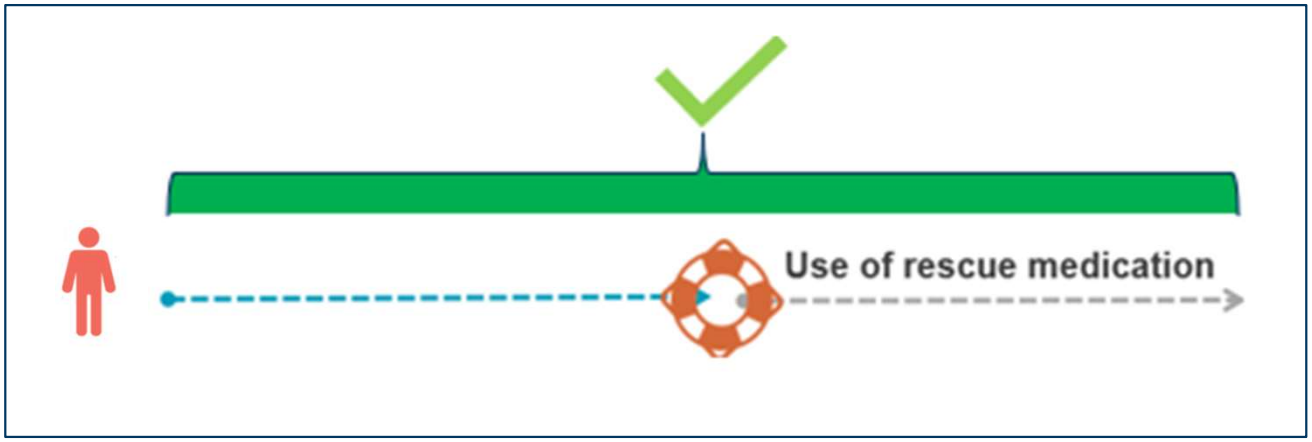


Treatment discontinuation because of toxicity



Strategies to handle ICEs: efficacy and safety

Treatment policy: The occurrence of the **ICE is irrelevant** w.r.t. the definition of the treatment effect of interest



- For the variable of interest, we will use the **values observed at wk24**, regardless of whether the participant is **rescued** or not
- We need to **collect data after the occurrence of the ICE**
- Failure to do so, **can prevent** implementing the treatment policy strategy

Strategies to handle ICES: efficacy and safety

Treatment policy (e.g., rescue): The **treatment effect of interest** is defined by the comparison **JAKib + rescue** *(for those who need it)* vs. **Placebo + rescue** *(for those who need it)*

Endpoint for Efficacy	Endpoint for Safety
Achieving remission at wk24	**Experiencing at least one RTI during the 24 weeks of study**

- This strategy is useful **IF** the **use of GCC** is **irrelevant** **OR** the **use of GCCs** is part of the **treatment regimen** that we want to evaluate
- In this example, **we can use the same strategy for efficacy and safety,** however **this is not true for other situations**
- The **Treatment Policy** estimates the **effect of being assigned** to a given **treatment BUT it does not estimate the true biological effect of the treatment** (pharmacologic response)

Strategies to handle ICES: efficacy and safety

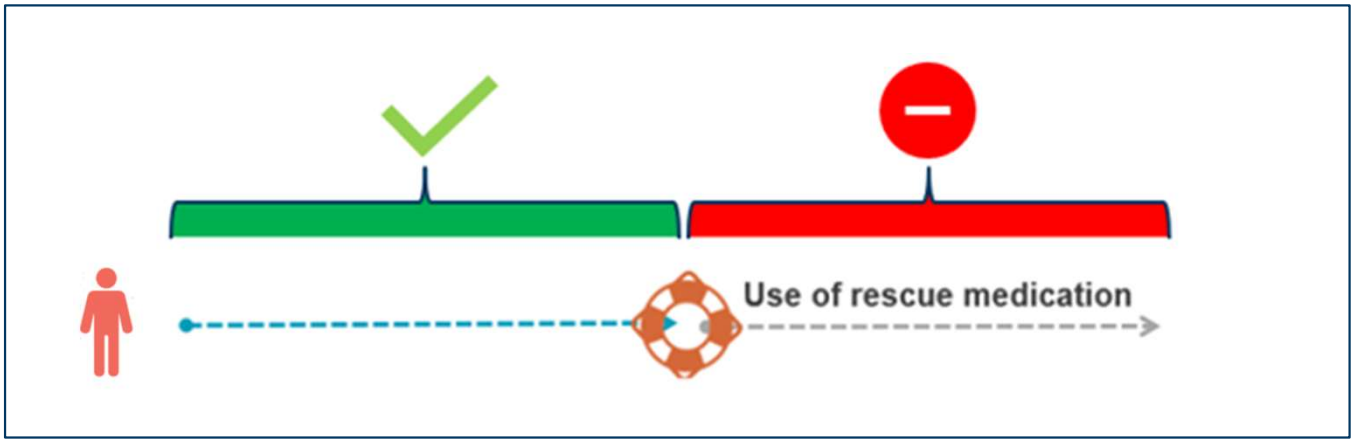
Treatment policy: Additional considerations for safety analyses

- The FDA tends to favor this strategy *("on-study") because it respects randomization*; **however,** it has some potential problems:
  1. If many more people use **rescue** in PBO than in JAKIB, then we will end up comparing **JAKIB vs rescue**
  2. If many more people **discontinue the JAKIB as compared to placebo,** we might **wrongly conclude** that the JAKIB is safe
- It could be **useful** to identify AEs with **long latency** that happen after treatment discontinuation (*e.g., malignancies*)

- *Hernán MA, Hernández-Díaz S.* ***Beyond the intention-to-treat in comparative effectiveness research****. Clin Trials. 2012*
- *Keene ON, Wright D, Phillips A, Wright M.* ***Why ITT analysis is not always the answer for estimating treatment effects in clinical trials****. Contemp Clin Trials. 2021*

Strategies to handle ICES: efficacy and safety

While on Treatment: We want to know the effect of **initiating** and **sustaining treatment before** the occurrence of the **ICE**



- Data after ICE are not used for the while on treatment analysis

Strategies to handle ICES: efficacy and safety

While on Treatment: The comparison of interest is **JAKib** vs. **PBO** until the end of the study and **before the occurrence of the ICE** *(e.g., rescue, treatment discontinuation)*

Endpoint for Efficacy	Endpoint for Safety
Achieving remission at wk24	**Experiencing at least one RTI during the 24 weeks of study**
• Patients who need **rescue** are in **High Disease Activity**; a **while on treatment analysis** will capture the **lack of efficacy** in the definition of the treatment effect *(i.e., treatment is **not adequate** for this patient)* • This is not always the case *(e.g., **Treatment Discontinuation** after toxicity issues while a patient is in **remission**)*	• **GCCs increase the risk of RTIs,** therefore **data after rescue** is not relevant to the treatment effect that I want to estimate *(JAKib vs PBO)* • Useful for AEs that **happen while** patients are **exposed to the drug** (*e.g., allergic reactions*) • Strategy very common in safety

Strategies to handle ICEs: efficacy and safety

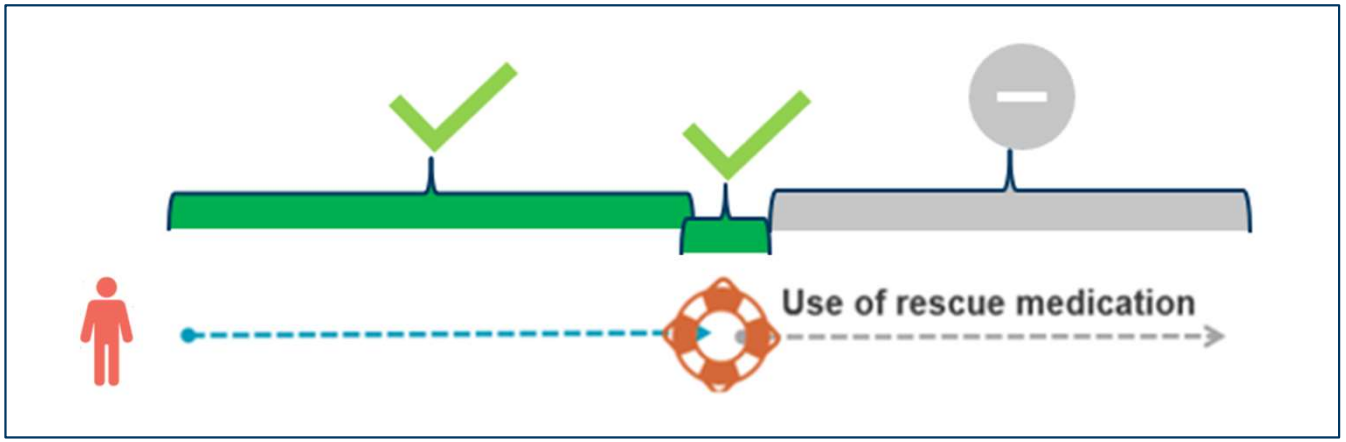
While on Treatment: Additional considerations for safety analyses

- On-treatment analyses can **underestimate** or **overestimate** the harms of the drug
- AEs with **long latency**
  - **AEs** that can happen after **treatment discontinuation**
  - *e.g., malignancies*
- AEs that are on the **same pathway**
  - ***Treatment discontinuation*** *after* ***myocardial fibrosis*** *will mask deaths as a consequence of* ***ventricular arrhythmias*** *that happen after Treatment Discontinuation*
  - *An on-treatment analysis would* ***underestimate*** *those deaths*

Yang F, Wittes J, Pitt B. ***Beware of on-treatment safety analyses****. Clin Trials. 2019*

Strategies to handle ICES: efficacy and safety

Composite: The treatment effect **integrates the ICE** in the definition of the variable (**composite endpoint)** indicating a **favorable** or **unfavorable** outcome



- Data after ICE are **not used**

Strategies to handle ICES: efficacy and safety

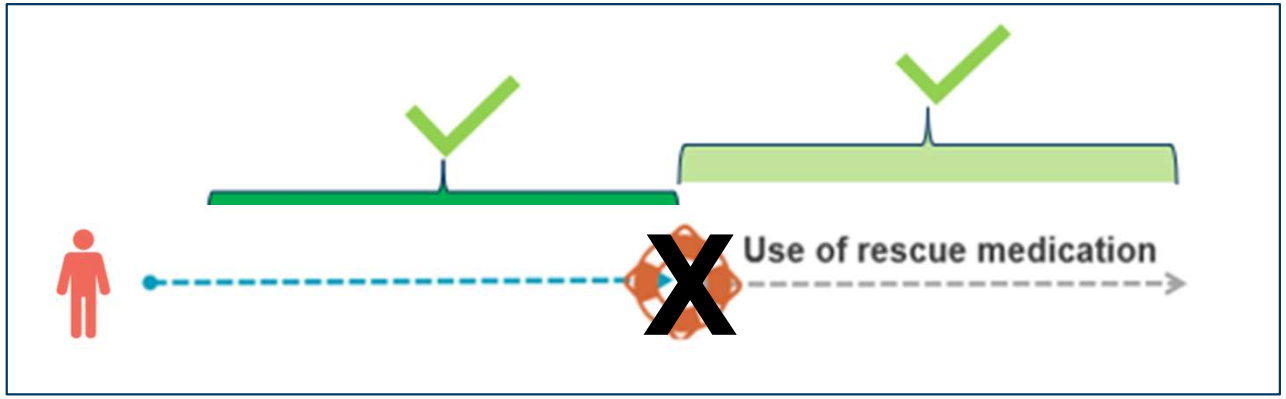
Composite (e.g., rescue): The comparison of interest is **JAKib** vs. **PBO**, but the **use of rescue** is considered **informative** to define the **endpoint of interest**

Endpoint for Efficacy	Endpoint for Safety
Achieving remission at wk24	**Experiencing at least one RTI during the 24 weeks of study**
• **Patients need rescue (GCC)** because the JAKib is **not effective** • We can consider that the use of rescue is a **treatment failure** and use Non-Responder Imputation **(NRI)**	• We **cannot impute a RTI to those patients** who use rescue (GCC)

- This example shows that sometimes we **cannot use the same strategy** **to define treatment effects** for **efficacy** and **safety**

Strategies to handle ICES: efficacy and safety

Hypothetical: We want to know the effect of **initiating treatment** and **adhering to the treatment regimen** defined in the protocol over the duration of the trial



- Physicians and patients may want to know the **treatment effect assuming complete adherence to protocol** and **NOT** an **average treatment effect** in a population in which **40% discontinued treatment**

Strategies to handle ICES: efficacy and safety

Hypothetical: The comparison of interest is **JAKib vs. PBO,** assuming that **everyone initiated** and **sustained the JAKib** compared to everyone **initiating** and **sustaining PBO** until the end of the trial

- Some *stakeholders consider hypothetical strategies not useful, however, they provide* ***useful information that helps to inform decisions***

Endpoint for Efficacy	Endpoint for Safety
Change from baseline in VAS-PAIN at wk 24	**Change from baseline in LDL-c at wk24**
• **Potential maximum** effect of the JAKib w.r.t. PAIN reduction at wk24 • **Maximum efficacy** *(optimistic)*	• Potential maximum effect of the JAKib w.r.t. increase in LDL-c at wk24 • **Maximum Toxicity** *(pessimistic)*

- *Hernán MA, Robins JM.* ***Per-Protocol Analyses of Pragmatic Trials****. N Engl J Med. 2017*
- *Mallinckrodt CH, Bell J, Liu G, Ratitch B, O'Kelly M, Lipkovich I, Singh P, Xu L, Molenberghs G.* ***Aligning Estimators With Estimands in Clinical Trials****: Putting the ICH E9(R1) Guidelines Into Practice. Ther Innov Regul Sci. 2020*

Summary and Conclusions

- Analysis of safety outcomes is **complex** *(it is more than frequency tables)*
- **Special considerations** in defining **treatment effects** for **safety outcomes**:

  - *Understand the **mechanism of action** of the **drug** under investigation*
  - *Understand the **pathophysiology** of the **AESI** under study:*
    - *Can we assume **constant hazard**? (e.g., Early onset vs. late onset)*
    - *Does the AESI happen **only when drug is being taken** or can it happen **after treatment discontinuation**? (e.g., Allergic reactions vs. malignancies)*
  - *Understand the safety profile of **rescue medications***

- Different **strategies** define **different treatment effects**
- We may need to use **different strategies** to fully characterize the safety profile
- The **strategy** defined for **efficacy** **does not dictate** the **strategy** for **safety**

Q&A

Many thanks for attending to this presentation!