

Advancing Safety Evaluation in Oncology Trials using Estimands

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Agenda



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6. Exposure Adjusted Incidence Rate (EAIR)
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8. Calculation of EAIR Based on the Proposed Frameworks
9. Conclusion

Estimand

Why ?

- A systematic and well-defined approach of clinical question of interest.
- Improves the study design, planning, execution and data collection.

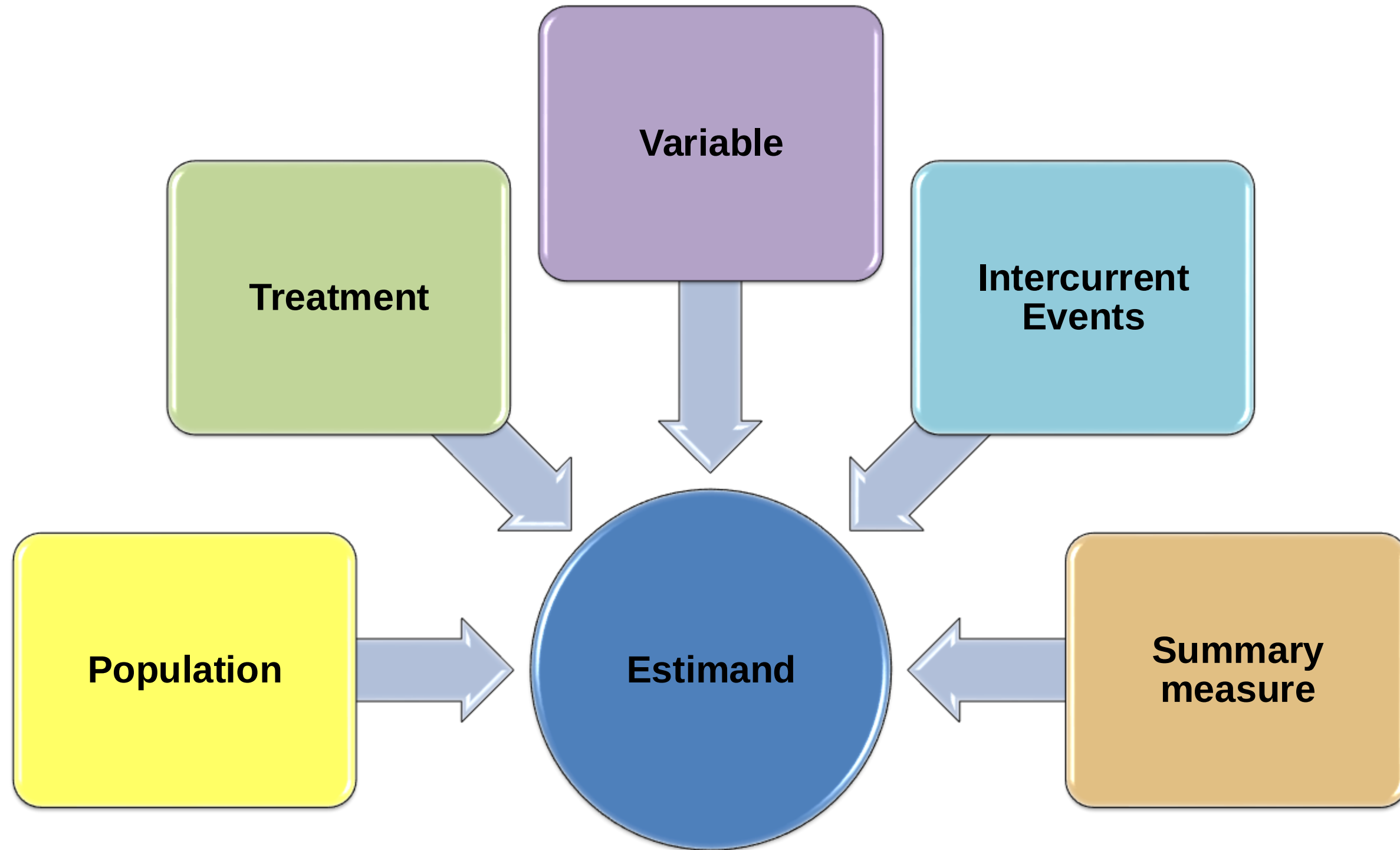
When ?

- ICH published E9 (R1) addendum on “Estimands and Sensitivity Analysis” in August 2017.

What ?

- Parameters to be estimated from clinical trial.
- Detailed information about each of Intercurrent Events (ICEs), Strategy to handle ICEs, population, variable and analysis.
- ICEs are events occurs after treatment initiation and will impact the endpoint (interchangeably used for clinical question of interest in this presentation).

Estimand Framework



Estimand Framework

- **Population** – Patients targeted by the clinical question
◆ **Who is included in the analysis?**
- **Treatment** – Treatment of interest and comparative treatment
◆ **What treatment groups are being compared?**
- **Variable (Endpoint)** – Parameter required to address the clinical question
◆ **What outcome is being measured?**
- **Intercurrent Events (ICEs)** – Events affecting the clinical question
◆ **How are ICEs like treatment discontinuation, death, or new therapies handled?**
- **Summary Measure** – Statistical method used for treatment comparison
◆ **How is the outcome summarized (e.g., mean, EAIR, hazard ratio)?**

Intercurrent Event (ICE) Strategies

Treatment Policy*

- Variable value will be considered despite of the ICE occurrence

Hypothetical

- Variable value after ICE would be statistically modelled and used for analysis

Composite

- Outcome of variable value will be affected based on the occurrence of ICE

While on Treatment*

- Variable value prior to ICE occurrence will be considered

Principal Stratum

- Variable value will be considered only for subset of patients from targeted population

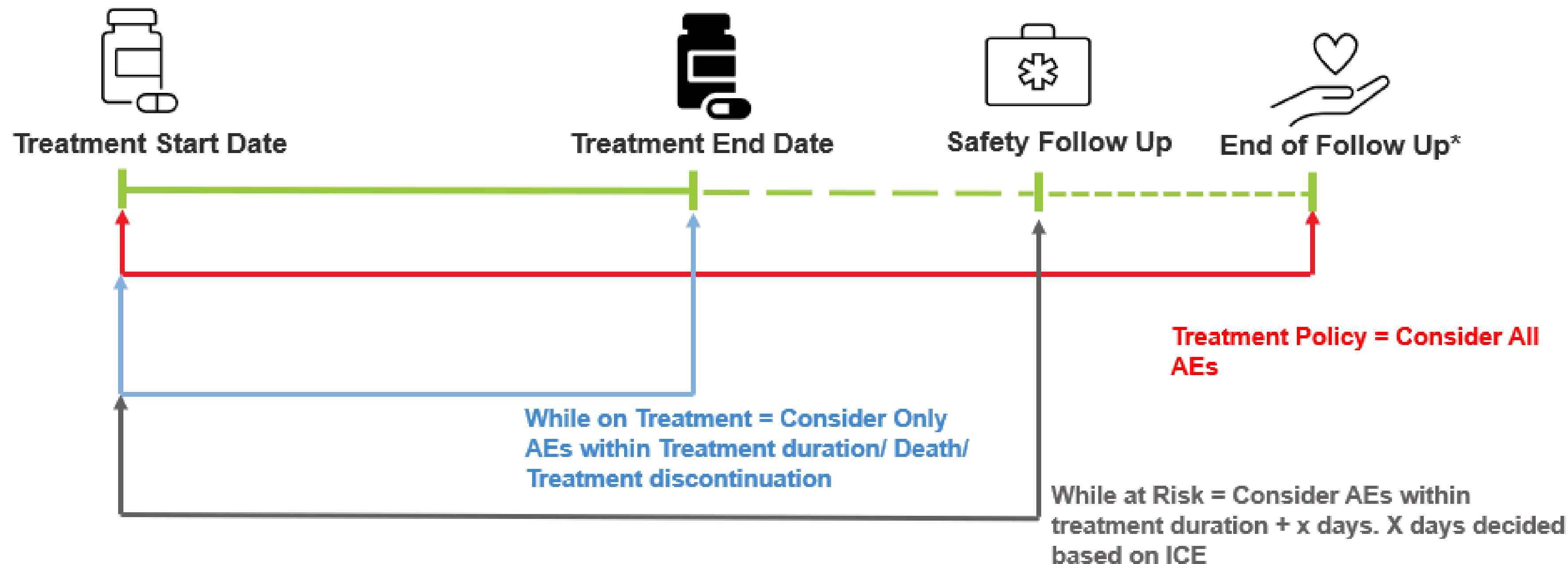
Key Differences Safety vs. Efficacy Estimands

Aspect	Safety Estimand	Efficacy Estimand
Population of Interest	Safety population vs. ITT population. Should safety follow ITT as per ICH E9(R1) for consistency?	ITT population is commonly used to ensure unbiased treatment effect estimation.
Variable (Endpoint)	Safety outcomes: Serious AEs, TEAEs, DLTs, lab results, vital signs.	Efficacy outcomes: Tumor response, survival, progression-free survival.
Intercurrent Events	Managing treatment discontinuation, new therapies. Should post-discontinuation AEs be included?	Managing events affecting treatment effect measurement (e.g., switching, rescue therapy).
Time Window	Defines how long safety events are collected (e.g., treatment + 30 days).	Efficacy endpoints often have predefined follow-up periods (e.g., OS, PFS).

Commonly used Safety Estimands Strategy

Strategy	AEs Considered	Handling of Treatment Discontinuation
Treatment policy	All AEs, regardless of treatment status	Includes all AEs
While-on-treatment	Only AEs during active treatment or till ICE	Excludes AEs after discontinuation/death
While-at-risk* [discussed in Wang et al in “Application of estimand framework in ICH E9 (R1) to safety evaluation”]	AEs during treatment and a specified period of time after treatment	Extends monitoring after discontinuation

Safety Estimands Strategy



* - Death / Withdrawal / Alive till FUP

Exposure Adjusted Incidence Rate (EAIR)

$$\text{EAIR} = \frac{\text{Number of subjects with events}}{\text{Total patient-years}}$$

Each subject's patient-years depend on whether they had an event:

With event:

$$\frac{\text{First event date} - \text{First dose date} + 1}{365.25}$$

Without event:

$$\frac{\text{Last study date} - \text{First dose date} + 1}{365.25}$$

The total patient-years is the sum of all subjects' patient-years.

Sample Estimand Framework

Question of Interest	Safety profile of the experimental treatment Vs the control treatment with respect to AEs observed for newly diagnosed patients with a certain type of metastatic cancer?
Population	Newly diagnosed patients with metastatic cancer
Treatment	Experimental Vs control treatment as defined in the protocol.
Variable (endpoint)	AEs or SAEs that are of clinical interest and that occur during study.
Population Level Summary	Difference in exposure-adjusted event rate of AEs

Intercurrent Event

- **While on treatment:**

Intercurrent Events (ICEs)	
	• Consider only AE/SAE occurred after treatment start till treatment end/death/treatment discontinuation.

- **Treatment Policy:**

Intercurrent Events (ICEs)	
	• Consider all AE/SAE occurred during entire study duration regardless of any ICEs like death or treatment discontinuation.

Intercurrent Event (Cont)



- While at Risk

Intercurrent Events (ICEs)	Event	Strategy
	AE:	
	Treatment discontinued but anti-cancer therapy not initiated.	Consider all AE started after treatment start till treatment discontinuation date+ 30 days
	Treatment discontinued but initiation of anti-cancer therapy	Consider all AE started after treatment start till minimum (treatment discontinuation date + 30 days, new therapy start date).
	SAE:	
	Treatment discontinued but anti-cancer therapy not initiated.	Consider all SAEs started after treatment start till treatment discontinued date + 90 days
	Treatment discontinued but initiation of anti-cancer therapy	Consider all SAEs started after treatment start date till new anti-cancer therapy start date+30.

EAIR Based on the Frameworks

Step 1: Derive Treatment Emergent Flag

Derive following treatment emergent flag in ADAE based on ICE strategy.

- **TRTEM1FL** – Derive treatment policy treatment emergent flag based on framework (a).
- **TRTEM2FL** – Derive while on treatment emergent flag based on framework (b).
- **TRTEM3FL** – Derive while at risk emergent flag based on framework (c).

EAIR Based on the Frameworks (Cont)

Step 2: Identify First Adverse Event for EAIR Calculation

- For subjects who experience an adverse event, only the first event that occurred will be considered in the calculation of patient-years.

Step 3: Determine Exposure Time for Each Subject

- For subjects with at least one event:

Exposure time = (Date of first event – First dose date + 1) / 365.25.

- For subjects without any event:

Exposure time = (Last dose date – First dose date + 31) / 365.25 for while at risk strategy

Exposure time = (Last dose date – First dose date + 1) / 365.25 for while on treatment strategy

Exposure time = (End of study date – First dose date + 1) / 365.25 for treatment policy strategy

EAIR Based on the Frameworks (Cont)

Step 4: Compute EAIR

- Compute EAIR for each event:

$$\text{EAIR} = \frac{\text{Total Number of Events}}{\text{Total Exposure Time (Patient-Years)}}$$

Step 5: Repeat for Different Strategies

- Perform Steps 4 and 5 for TRTEM2FL and TRTEM3FL to calculate EAIR based on:

While on Treatment Strategy (TRTEM2FL)

While at Risk Strategy (TRTEM3FL).

EAIR - Treatment Policy Vs While on Treatment Vs While at Risk

Exposure Adjusted Incidence Rate by System Organ Class and Preferred Term for Treatment A

System Organ Class	Preferred Term	Treatment A					
		Treatment Policy		While on Treatment		While at Risk	
		n [a]	EAIR [b]	n [a]	EAIR [c]	n [a]	EAIR [d]
GASTROINTESTINAL DISORDERS	ABDOMINAL DISCOMFORT	1	3.58	1	4.54	1	3.58
	ABDOMINAL PAIN	1	3.63	0	0.00	0	0.00
	DIARRHOEA	3	11.02	3	13.97	3	11.02
	DYSPEPSIA	1	3.84	0	0.00	0	0.00
	GASTROINTESTINAL HAEMORRHAGE	1	3.55	0	0.00	0	0.00
	HIATUS HERNIA	1	3.56	0	0.00	1	3.56
	NAUSEA	6	22.40	4	18.50	5	18.36
	SALIVARY HYPERSECRETION	4	15.04	4	19.11	4	15.04
	STOMACH DISCOMFORT	1	3.58	1	4.54	1	3.58
	VOMITING	6	21.78	1	4.56	3	10.82

[a] n= Number of subjects with events. A subject is counted only once for multiple events within a System Organ Class and Preferred Term.

[b] EAIR implemented using 'Treatment Policy' strategy

[c] EAIR implemented using 'While-on-treatment' strategy

[d] EAIR implemented using 'While-at-risk' strategy

EAIR - Treatment Policy Vs While on Treatment Vs While at Risk (Cont)

The output suggests

- Treatment policy strategy may overestimate the EAIR,
 - While on treatment strategy could underestimate the rate,
 - While at risk strategy, when carefully defining the risk window, proves to be an effective approach for safety analysis.
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- The yellow-highlighted rows in table 1 indicate differences in the number of subjects with at least one occurrence of an event in each strategy.

Conclusion

Our observation based on the above table using sample AE data.

- Treatment Policy, While on Treatment, and While at Risk strategies impact EAIR calculations differently.
- While at Risk: A Balanced Approach
 - This method refines safety assessments by incorporating a risk window,
 - capturing relevant AEs while minimizing risk overestimation or underestimation.
 - Offers a more precise alternative between Treatment Policy and While on Treatment strategies.
- Further exploration of the While at Risk strategy is necessary to maximize its benefits in safety analysis.



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