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Advancing Safety Evaluation in Oncology Trials using Estimands

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ABSTRACT

In Oncology trials, ensuring patient safety is as crucial as evaluating treatment efficacy. Traditional safety assessment methods can introduce biases, potentially misleading the drug's safety profile and risk-benefit ratio. This paper investigates the application of estimands to safety data to address these challenges. We focus on the Exposure-Adjusted Incidence Rate (EAIR), a methodology that provides more accurate comparisons between treatment groups with varying exposure durations. Integrating EAIR with the estimand framework enhances the precision and reliability of safety evaluations.

This paper presents an implementation strategy, addresses key challenges, and highlights the framework's potential to enhance safety data interpretation in oncology trials. By comparing EAIRs, we can determine the impact of intercurrent events on incidence rates. Significant differences between these rates may highlight the influence of intercurrent events on the study outcomes.

INTRODUCTION

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) published E9 R1 "Addendum on Estimands and Sensitivity Analysis in Clinical Trials" in August 2017. An estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective. Description of estimands must be based on how intercurrent events affect clinical question of interest. Intercurrent events (ICE) are events occurring after treatment start and how it affects either the interpretation or measurement associated with clinical questions of interest. Some of examples of ICEs are Death, switch to other treatment, treatment discontinuation etc. There are five strategies for addressing ICEs like Treatment policy strategy, Hypothetical strategies, Composite variable strategies, While on treatment strategies and Principal stratum strategies. After regulatory authorities endorsed it from 2020, Estimands gained more popularity and included in Statistical Analysis Plan (SAP). It was widely used in ephicacy analysis, but we are trying to use it in safety analysis.

The estimands primarily focus on assessing efficacy in randomized clinical trials and estimands have largely been discussed within this context. However, their application to safety assessments remains relatively unexplored. While efficacy and safety estimands share some similarities, they differ in key aspects, particularly in handling intercurrent events such as treatment discontinuation or the initiation of new therapies. These events can significantly impact safety outcomes, requiring a tailored approach. Expanding the estimand framework to safety evaluations can improve the accuracy, consistency, and clinical relevance of safety analyses in oncology trials.

The application of estimands in safety analyses for oncology trials, with a focus on Exposure-Adjusted Incidence Rate (EAIR). We discuss key considerations, including the choice of safety population, the application of the "while on treatment" Vs "while at risk" [1] intercurrent event strategy, and the development of a structured EAIR framework. Through this approach, we aim to demonstrate how estimands enhance the accuracy of safety evaluations, ensuring a more comprehensive understanding of treatment-related risks in oncology.

1. Estimands and Intercurrent Events (ICEs):

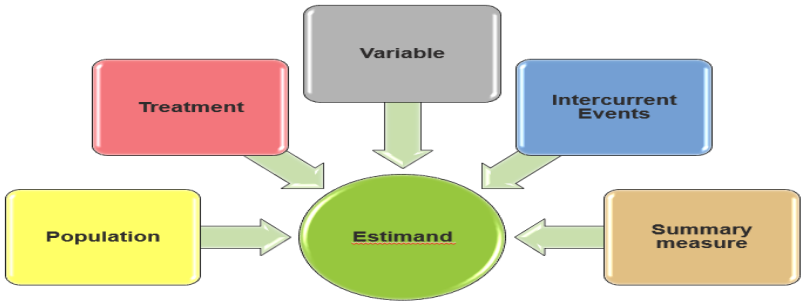
Estimands provide a unified framework to define, interpret, and align clinical trial objectives with statistical analyses.
Estimands framework enables proper trial planning that clearly distinguishes between the target of estimation (trial objective, estimand), the method of estimation (estimator), the numerical result and a sensitivity analysis.

Estimand Attributes:

1. **Population:** Patients targeted by the clinical question.
2. **Treatment:** Treatment of interest and comparative treatment.
3. **Variable (or endpoint):** Parameter of patients that is required to address the clinical question.

4. **Intercurrent Event:** List of ICEs which will affect clinical question and strategy used to address it.
5. **Summary Measure:** Summary statistics used for treatment comparison.

Figure 1: Estimand Attributes



Strategies for Addressing Intercurrent Events:

1. **Treatment Policy Strategy:** Variable value will be considered despite of the ICE occurrence.
2. **Hypothetical Strategy:** Assumes ICE would not occur to patients. Variable value after ICE would be statistically modelled (multiple imputation or other missing data handling) and used for analysis.
3. **Composite Strategy:** Outcome of variable value will be affected based on the occurrence of ICE.
4. **While on Treatment Strategy:** Variable value prior to ICE occurrence will be considered.
5. **Principal Stratum Strategy:** Variable value will be considered only for subset of patients from targeted population.

2. Key Differences in Defining Safety vs. Efficacy Estimands:

When developing safety estimands, several critical factors must be considered when compared to efficacy:

- **Population of interest:** Determining whether the safety analysis focus on the safety population, ITT population, or subsets. In principle, the target population for safety and efficacy assessments is often the same. However, the actual population analyzed for safety might differ from the efficacy analysis set, such as the "Intent to Treat" (ITT) population. The population attribute in a safety estimand is about clearly defining who is included in the safety analysis and ensuring that the analysis set is appropriate for answering the safety question of interest. The ITT set is the typical analysis set, but careful consideration of the target population is crucial for proper interpretation of safety findings, and for informing decisions with respect to the overall target population.

- **Treatment:** Aligning with efficacy estimands, the treatment variable includes the investigational therapy and its comparator as defined in the study protocol.

- **Variable (endpoint):** Which safety outcomes to evaluate (e.g., serious AEs, treatment-emergent AEs, dose-limiting toxicities, laboratory test results, vital signs).

- **Intercurrent events:** Managing scenarios such as treatment discontinuation or initiation of subsequent therapies. Should AEs occurring post-discontinuation be included in the safety profile?

- **Defining an appropriate time window** for capturing safety data (e.g., during treatment plus 30 days post-treatment).

3. Commonly Used Strategies for Safety Estimands:

Intercurrent events and their handling strategies are discussed extensively in E9 (R1) with a focus on efficacy. Examples of intercurrent events for safety, similar to those for efficacy, include treatment discontinuation or switch, rescue medication or concomitant medication, death, or other events that either prevent the event of interest from occurring or change the variable value. However, the implementation of the strategies could be different between a safety estimand and an efficacy estimand. The two strategies, “treatment policy” and “while-on-treatment” and are the most well-known and popular approaches for safety endpoints. Wang et al in “Application of estimand framework in ICH E9 (R1) to safety evaluation” [1] proposed another strategy “while at risk”, which is a compromise between treatment policy and while-on-treatment strategies for safety analysis.

It must be determined whether adverse events (AEs) need to be monitored after treatment discontinuation, which is influenced by the drug's mechanism of action. AEs that occur too far away from the treatment discontinuation might now be considered due to the potential difficulty in determining relationship with study treatment. If we use while on treatment strategy only on treatment AEs will be considered. AEs after treatment discontinuation will not be considered. This will either underestimate or overestimate the risk of the drug. So based on drug mechanism and study duration, on-treatment analysis adverse events + x days can be considered.

The "while at risk" framework evaluates safety outcomes during the treatment period, extending the observation window by an additional +x days to capture any delayed treatment effects. If a subject discontinues treatment but experiences an adverse event within the +x days risk window, it is counted towards the treatment's safety profile.

Considerations:

- Defining +x days based on pharmacokinetics or biological rationale for treatment effects.

- Ensuring a balance between capturing relevant safety data and avoiding confounding effects from subsequent treatments.

- For AEs occurring after rescue medication or treatment switching, clinical judgement should be utilized to assess causal relationship between those AEs and the treatment(s).

- Detailed discussions with clinicians and physicians on AE monitoring after those intercurrent events are needed.

- Data collection plan for AE should be devised during study planning phase.

Let's discuss three main strategies below for handling intercurrent events when assessing safety outcomes: while-on-treatment, while-at-risk, and treatment policy. These strategies affect how adverse events (AEs) are included in the analysis, particularly in relation to treatment discontinuation or other events that interrupt a patient's treatment.

4. Treatment Policy Strategy:

Definition: The treatment policy strategy includes all AEs, regardless of whether intercurrent events occur. The safety endpoints are collected and used no matter whether intercurrent events occur or not.

Example: If a study monitors cardiovascular risk, AEs could be monitored for an extended follow-up even if participants have discontinued treatment.

Limitations:

- May introduce bias and change the interpretation of a safety endpoint13.
- May overestimate risk, especially when alternative treatments with higher risk are used after discontinuing the original treatment.

5. While on Treatment Strategy:

Definition: The while on treatment strategy only considers AEs that occur while the patient is actively receiving the study treatment2. Any AEs occurring after treatment discontinuation are not included in the analysis.

Example: In a clinical trial, if a patient receives a drug for 100 days and experiences an AE on day 50, the exposure time is 50 days, and the event will be considered. If another patient experiences the same AE on day 120, but treatment was discontinued on day 100, that event is not counted, and the exposure time is 100 days

Limitations:

- May introduce bias by ignoring events that occur after treatment discontinuation, potentially underestimating or overestimating the risk.
- Not recommended for long-term safety monitoring.

6. While at Risk Strategy:

Definition: The while at risk strategy is a compromise between the while-on-treatment and treatment policy approaches. It defines a monitoring window for AEs from the start of treatment up to a specified period after the last dose.

Example: In an oncology trial, the "while-at-risk" period may include all AEs occurring during treatment and up to 30 days after treatment, or 90 days for serious AEs.

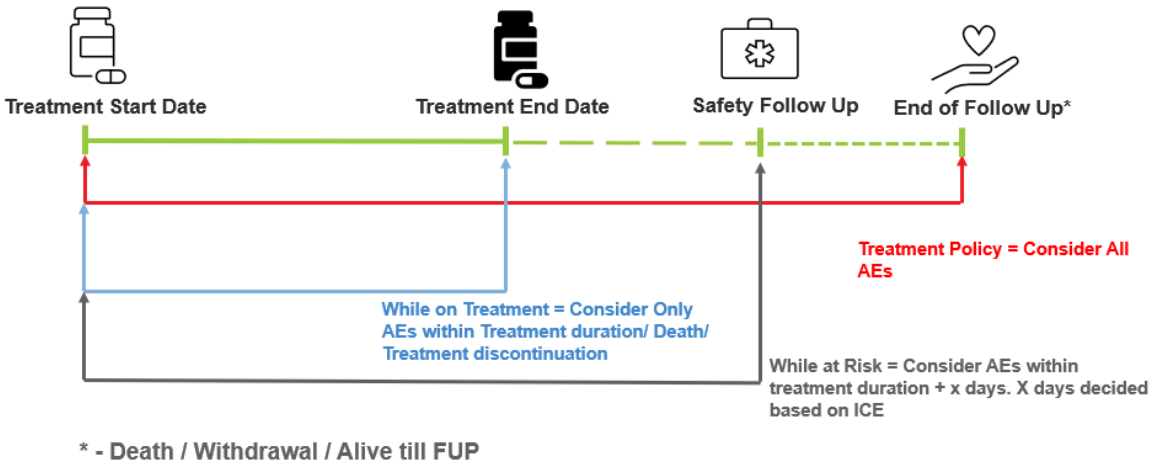
Application: The monitoring window is extended after the treatment discontinuation to capture potential carry-over effects of the experimental treatment.

Considerations: Clinical judgment should be used to assess the causal relationship between AEs and treatment after events like rescue medication or treatment switching.

7. Summary of Strategies for Adverse Event analysis:

Strategy	AEs Considered	Handling of Treatment Discontinuation	Use Cases	Limitations
Treatment policy	All AEs, regardless of treatment status	Includes all AEs	Simple to measure, maintains randomization	May overestimate risk, can introduce bias, may change interpretation of safety endpoints
While-on-treatment	Only AEs during active treatment	Excludes AEs after discontinuation	Short-term risk assessment, symptom-relieving drugs, when association is difficult to establish	May underestimate risk, ignores post-treatment events, not recommended for long-term monitoring
While-at-risk	AEs during treatment and a specified period of time after treatment	Extends monitoring after discontinuation	When safety events are affected by total exposure, when follow-up is equal between treatment arms.	Requires careful definition of "at-risk" period.

Figure 2: Pictorial Representation of strategies.



8. EAIR: A Framework for Implementation

The Exposure-Adjusted Incidence Rate (EAIR) is a critical metric for oncology safety evaluation, particularly in trials where treatment duration varies across patients. It is used to standardize the risk of an AE per unit of time with constant hazard is assumed. EAIR allows for a consistent comparison of adverse event rates relative to patient exposure time, addressing biases that arise from differential exposure. EAIR is best used when follow-up times vary between patients, and when it is important to account for the actual time of exposure to a treatment, under the assumption that the risk is constant over time. It is a standardized measure of risk per unit time, suitable for comparisons across treatment groups

or pooled data. However, it is important to be aware of its assumptions and limitations, and to consider other methods, such as time-to-event analyses, when the risk of an AE is not constant over time, or in the presence of competing risks. In this paper, we will use Exposure-Adjusted Incidence Rate (EAIR) for comparing Treatment policy, While-on-treatment and While-at-risk strategies.

EAIR Formula:

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

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.

9. Development of a Sample Framework for EAIR:

The estimand framework discussed by X. Wang et al. in "Application of estimand framework in ICH E9 (R1) to safety evaluation" [1] [1] is applied to evaluate the exposure-adjusted incidence rate (EAIR) in oncology trials. This framework ensures a structured approach to handling intercurrent events and defining appropriate safety estimands.

a. Estimand Framework based on Treatment Policy Strategy:

Question of Interest	What is the safety profile of the experimental treatment versus the control treatment (with respect to the difference in exposure-adjusted event rate of specific group of AEs for newly diagnosed patients with a certain type of metastatic cancer?
Population	Newly diagnosed patients with metastatic cancer as defined by the protocol inclusion and exclusion criteria
Treatment	The experimental treatment and the control treatment as defined in the protocol
Variable (endpoint)	The specific group of AEs or SAEs that are of clinical interest and that occur during study.
Intercurrent Events (ICEs)	Consider all AE/SAE occurred during study regardless of any ICE like death or treatment discontinuation.
Population Level Summary	Difference in exposure-adjusted event rate of AEs (experimental treatment vs. the control treatment)

b. Estimand Framework based on while on treatment Strategy:

Question of Interest	What is the safety profile of the experimental treatment versus the control treatment (with respect to the difference in exposure-adjusted event rate of specific group of AEs observed during treatment for newly diagnosed patients with a certain type of metastatic cancer?
Population	Newly diagnosed patients with metastatic cancer as defined by the protocol inclusion and exclusion criteria
Treatment	The experimental treatment and the control treatment as defined in the protocol.
Variable (endpoint)	The specific group of AEs or SAEs that are of clinical interest and that occur during study.
Intercurrent Events (ICEs)	Death and treatment discontinuation are considered as intercurrent event. Consider only AE/SAE occurred after treatment start till treatment end or death or treatment discontinuation.
Population Level Summary	Difference in exposure-adjusted event rate of AEs (experimental treatment vs. the control treatment)

c. Estimand Framework based on While at Risk Strategy:

Question of Interest	What is the safety profile of the experimental treatment versus the control treatment (with respect to the difference in exposure-adjusted event rate of specific group of AEs observed during treatment and until 30 days after end of treatment or 30 days after end of treatment if the patient initiates new anti-cancer therapy, whichever occurs first) for newly diagnosed patients with a certain type of metastatic cancer?	
Population	Newly diagnosed patients with metastatic cancer as defined by the protocol inclusion and exclusion criteria	
Treatment	The experimental treatment and the control treatment as defined in the protocol	
Variable (endpoint)	The specific group of AEs or SAEs that are of clinical interest and that occur during study treatment and until 30 days after end of treatment (or 90 days after end of treatment if AEs are serious)	
Intercurrent Events (ICEs)	***Event***	***Strategy***
	AE:	
	Treatment discontinued but anti-cancer therapy not initiated.	While at risk strategy. Consider all AE started after treatment start till treatment discontinuation date+ 30 days
	Treatment discontinued but initiation of anti-cancer therapy	While at risk strategy. 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.	While at risk strategy. Consider all SAEs started after treatment start till treatment discontinued date + 90 days
	Treatment discontinued but initiation of anti-cancer therapy	Use While at risk strategy. Consider all SAEs started after treatment start date till new anti-cancer therapy start date+30.
Population Level Summary	Difference in exposure-adjusted event rate of AEs (experimental treatment vs. the control treatment)	

10. Calculation of EAIR Based on the Proposed Frameworks

Step 1: Derive following treatment emergent flag in ADAE.

- 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).

Note: DCFL – Subject Discontined Flag (N= No; Y=Yes); NEWTHEDT – New Anti Cancer Therapy Date;

```
/* DERIVE TREATMENT POLICY TREATMENT EMERGENT FLAG */
IF NOT MISSING(ASTDT) THEN TRTEM1FL="Y";

/* DERIVE WHILE ON TREATMENT TREATMENT EMERGENT FLAG */
IF NOT MISSING(ASTDT) AND ASTDT>=TRTSDT AND  ASTDT<=TRTEDT THEN TRTEM2FL="Y";

/* DERIVE WHILE AT RISK TREATMENT EMERGENT FLAG */
IF NOT MISSING(ASTDT) THEN DO;
    IF AESER = "N" THEN DO; /* NON SERIOUS AE */
        IF DCSFL="Y" AND NOT MISSING(NEWTHEDT) THEN DO; /* TREATMENT DISCONTINUED BUT STARTED NEW ANTI CANCER THERAPY */
            IF ASTDT>=TRTSDT AND ASTDT <= min(TRTEDT+30,NEWTHEDT) THEN DO; TRTEM3FL="Y"; END;
        END;
        ELSE DO; /* TREATMENT COMPLETED OR TREATMENT DISCONTINUED BUT NO NEW ANTI CANCER THERAPY */
            IF ASTDT>=TRTSDT AND ASTDT <=TRTEDT+30 THEN DO; TRTEM3FL="Y"; END;
        END;
    END;
    IF AESER = "Y" THEN DO; /*SERIOUS AE */
        IF DCSFL="Y" THEN DO; /* TREATMENT DISCONTINUED */
            IF NOT MISSING(NEWTHEDT) THEN DO; /* NEW ANTI CANCER STARTED */
                IF ASTDT>=TRTSDT AND  ASTDT<=TRTEDT+30 THEN DO; TRTEM3FL="Y"; ;END;
            END;
        END;
        IF MISSING(DCSFL) AND (DCSFL="Y" AND MISSING(NEWTHEDT)) THEN DO; /* TREATMENT COMPLETED OR TREATMENT DISCONTINUED */
            IF ASTDT>=TRTSDT AND  ASTDT<=TRTEDT+90 THEN DO; TRTEM3FL="Y"; TRTEM3FL_Y="Y";END;
        END;
    END;
END;
```

Step 2: Create the input dataset for EAIR by merging ADSL and ADAE where TRTEM1FL="Y" to get EAIR based on treatment policy, selecting only subjects where SAFFL = "Y."

Step 3: Create dummy dataset which includes all subjects from ADSL, AEBODSYS and AEDECOD from ADAE.

Step 4: For subjects who experience an adverse event, only the first event that occurred will be considered in the calculation of patient-years.

Step 5: Calculate Exposure Time for Each Subject by merging DUMMY, FIRST_AE and ADSL dataset.

- 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 study date – First dose date + 1) / 365.25.

Step 6: Compute EAIR for each event by dividing the total number of events by the total exposure time (patient -years).

Step 7: Repeat Step 4 to Step 5 for TRTEM2FL and TRTEM3FL to get EAIR based on While on Treatment and While at Risk strategy.

The output below suggests that the treatment policy strategy may overestimate the EAIR, while the while on treatment strategy could underestimate the rate. However, the while at risk strategy, when carefully defining the risk window, proves to be an effective approach for safety analysis.

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.

Table 1 : Exposure Adjusted Incidence Rate based on Treatment Policy Vs While on Treatment Vs While at Risk.

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

		Treatment A					
		Treatment Policy		While on Treatment		While at Risk	
System Organ Class	Preferred Term	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

7. Conclusion

In this paper, we implemented three different safety analysis strategies: two ICH-defined approaches Treatment Policy and While on Treatment and the newly proposed While at Risk strategy, using sample adverse event (AE) data assessed with the EAIR methodology. Our observations suggest that the While at Risk approach offers a more balanced assessment compared to the other two strategies. A comparison of these strategies highlights differences in incidence rates, underscoring the importance of selecting an appropriate approach based on study objectives and risk considerations. This methodology can be extended to other safety analyses as needed. Further exploration of the While at Risk strategy is necessary to refine its implementation and enhance its applicability across various oncology trial settings.

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