PharmaSUG China 2025 - Paper DS-107

# Implementation of the Estimand Framework to Oncology Project with Time-to-Event Endpoints

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## ABSTRACT

During clinical trials, different stakeholders—such as regulatory authorities, sponsors, patients, and physicians—may have varying perspectives on the drug's treatment effects. Therefore, defining the primary objectives and therapeutic effects in advance is critical to achieving consensus among all parties involved. This alignment is essential for the planning, design, execution, and analysis of clinical trials. For this reason, ICH E9(R1) introduced a structured framework to enhance dialogue among all stakeholders involved in defining the objectives, design, conduct, analysis, and interpretation of clinical trials—as well as discussions between sponsors and regulatory authorities regarding the key clinical questions the trial should address. Since the release of ICH E9(R1), an increasing number of pharmaceutical companies have adopted the Estimand framework for data analysis. Concurrently, Whitepaper has been published on implementing the standard data structure for Estimands, along with corresponding data specifications. While use cases in non-oncology projects have been widely shared within the industry, the implementation in oncology projects—where time-to-event endpoint data lacks intermediate records—remains less discussed. This article elaborates on how to apply the framework in such contexts.

## INTRODUCTION

Intercurrent events can be categorized into three types: Treatment discontinuation, Additional/alternative treatment and Terminal events. The discussion in this article is primarily based on Initiation of new anti-cancer therapies and Treatment discontinuation.

Permitting patients to receive new anti-cancer therapies (such as chemotherapy, targeted therapy, or immunotherapy) typically involves a careful balance of scientific, ethical, and practical considerations. When patients receive additional anti-cancer treatments during the trial, these interventions may potentially confound the evaluation of the investigational drug's true therapeutic effect. The difference from prohibited medications in non-oncology trials lies in the fact that in oncology studies, once new anti-cancer therapy is administered, it impacts subsequent efficacy evaluations, whereas in non-oncology trials, prohibited medications—especially short-acting drugs—may affect outcomes during a specific period.

Suggested by industry groups, there is a single dataset named ADICE gathering all intercurrent events in one place. When possible, the ADSL and ADICE datasets are built at the beginning of the analysis data flow to serve as support for documenting the impact of intercurrent events into the other ADaM datasets supporting the statistical analyses, though more complex situations can occur.

Considering the characteristics of new anti-cancer therapy's effect on time-to-event endpoints in oncology studies, this paper recommends including the initial instance of new anti-cancer therapy in the ADICE dataset.

## IMPLEMENTATION OF ESTIMAND IN CASE STUDY

We will now illustrate the implementation of standard datasets within the Estimand framework using a concrete case study.

| | | |
|---|---|---|
| Treatment | Investigational Product vs. Control | |
| Population | mCRPC subjects | |
| Variable | BIRC PFS (based on RECIST v1.1) | |
| Intercurrent Events and Handling | Intercurrent Events: | Strategies: |
| | Discontinuation of treatment | Treatment Policy Strategy, collect and include the subsequent data even if the subject discontinues treatment. |
| | Start new anti-cancer therapy | Hypothetical Strategy, collect and include the data until the subject begins new anti-cancer therapy. |
| Population-level Summary | Hazard ratio, investigational product group vs. control group. | |

**Table 1 Definition of Primary Estimand**

| | | |
|---|---|---|
| Treatment | Investigational Product vs. Control | |
| Population | mCRPC subjects | |
| Variable | OS | |
| Intercurrent Events and Handling | Intercurrent Events: | Strategies: |
| | Discontinuation of treatment | Treatment Policy Strategy, collect and include the subsequent data even if the subject discontinues treatment. |
| | Start new anti-cancer therapy | Treatment Policy Strategy, collect and include the subsequent data even if the subject begins new anti-cancer therapy. |
| Population-level Summary | Hazard ratio, investigational product group vs. control group. | |

**Table 2 Definition of Secondary Estimand**

## SUBJECT-LEVEL EXAMPLES OF INTERCURRENT EVENTS HANDLING

Upon receiving the Statistical Analysis Plan (SAP), programmer can begin developing procedures to organize relevant datasets. The SAP should contain precise and unambiguous descriptions of intercurrent events.

For estimands with PFS as the target variable, initiation of new anti-cancer therapy refers to treatments occurring before BIRC-assessed PD;

For estimands with OS as the target variable, it refers to treatments initiated before death (noting that no new anti-cancer therapy can occur post-mortem).

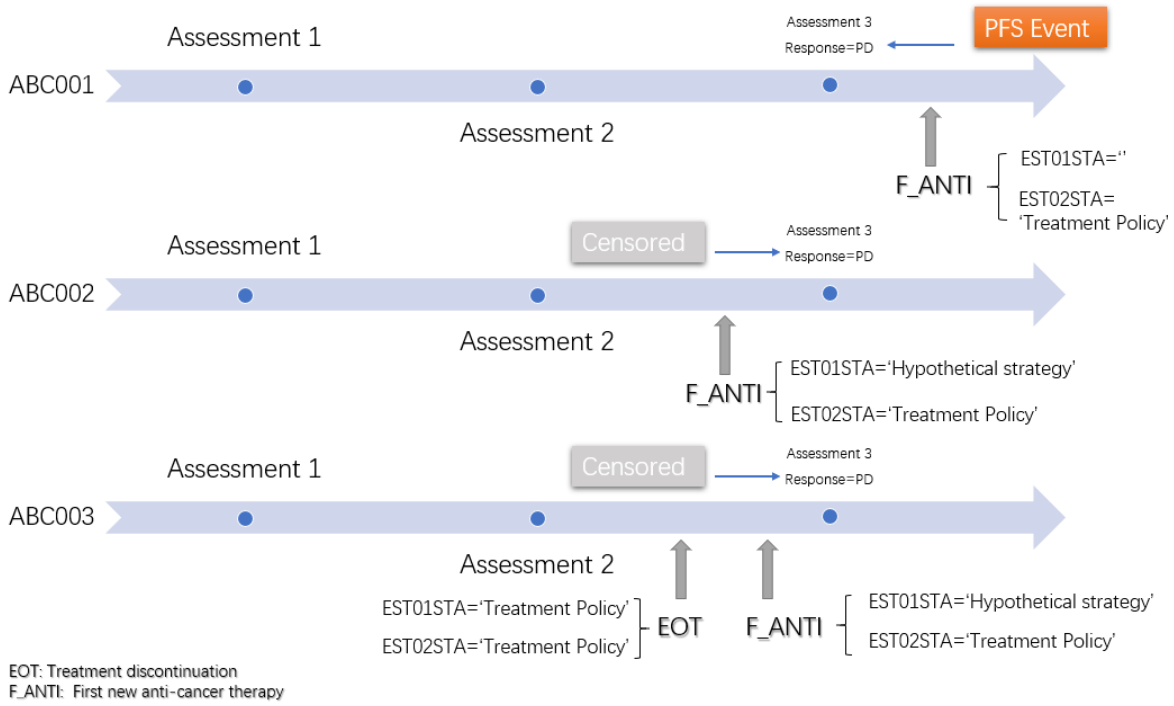


**Figure 1. Subjects process in case study**

**Subject ABC001**

Intercurrent Event: Received new anti-cancer therapy
Primary Estimand (PFS):
Strategy: Blank
Rationale: Therapy initiated after PFS event → No impact on PFS endpoint
Secondary Estimand (OS):
Strategy: Treatment Policy
Rationale: Therapy initiated before death → Impacts on OS endpoint

**Subject ABC002**

Intercurrent Event: Received new anti-cancer therapy
Primary Estimand (PFS): Hypothetical (therapy pre-progression)
Secondary Estimand (OS): Treatment Policy (therapy pre-death)

**Subject ABC003**

Intercurrent Event 1: Treatment discontinuation
Both Estimands: Treatment Policy
Rationale: Discontinuation reflects real-world clinical practice
Intercurrent Event 2: New anti-cancer therapy (Radiotherapy)
Primary Estimand (PFS): Hypothetical
Secondary Estimand (OS): Treatment Policy
Rationale: Therapy initiated before PFS event → Impacts both PFS and OS analyses

## IMPLEMENTATION OF ESTIMANDS IN ADICE

With the SAP estimands confirmed, the first step is to create the intercurrent events dataset (ADICE), which consolidates all protocol-defined intercurrent events. Key considerations:

Treatment Episodes: While subjects may receive multiple new anti-cancer therapies, only the first occurrence needs inclusion for most analyses, as initial therapy changes are clinically most relevant for oncology studies.

Variable Consistency: The ATERM/ADECODy/ACATy fields should maintain consistent descriptions across records. The critical differentiators are the ESTzzSTP/ESTzzSTA variables (where "zz" represents the estimand number), which specifies the handling strategy (e.g., hypothetical, treatment policy) for each intercurrent event within that estimand's framework.

| Variable Name | Variable Label | Core | CDISC Notes |
|---|---|---|---|
| USUBJID | Unique Subject Identifier | Req | DM.USUBJID |
| ASEQ | Analysis Sequence Number | Perm | Sequence number given to ensure uniqueness of subject records within an ADaM dataset. |
| ATERM | Analysis Term | Req | Analysis term describing the intercurrent event. A more granular description of the intercurrent event, close to the source. |
| ADECODy | Analysis Term Coded y | Perm | Source coding, single source, useful to support. -- DECOD/UDECOD are mutually exclusive. |
| ACATy | Analysis Category y | Req | Categorisation of the intercurrent events. Useful when there are different levels of granularity of intercurrent event across estimands. |
| ASTDT | Analysis Start Date | Req | Source start date of the intercurrent event in numerical format. One of ASTDT/ASTDTM must be present. |
| AENDT | Analysis End Date | Perm | Source end date of the intercurrent event in numerical format. Included if the |

| | | | |
|---|---|---|---|
| | | | intercurrent event end-date is relevant to assess the impact of the intercurrent event on datapoints. |
| ESTzzSTP | Estimand zz planned handling strategy | Req | Documents the planned strategies for handling the intercurrent events related to estimand zz*, as described in the protocol and/or analysis plan. Blank if the intercurrent event is not related to estimand zz. |
| ESTzzSTA | Estimand zz actual handling strategy | Req | Documents the actual strategies for handling the intercurrent events related to estimand zz. Blank if the intercurrent event is not related to estimand zz or if the intercurrent event handling strategy is masked by the strategy of another intercurrent event that has a higher precedence. Initially, ESTzzSTA is filled as ESTzzSTP. Then, in a second step, the other intercurrent events for the same estimand are considered, subject by subject, along with their strategy and priority rules. Typically, for a given subject, if an intercurrent event is preceded by another one AND that one has a higher precedence in terms of handling strategy, the handling strategy of that intercurrent event will prevail and mask the strategy of the current intercurrent event. In that case, ESTzzSTA of that event will be set to blank. Note that priority rules are decided and |

| | | | |
|---|---|---|---|
| | | | documented by the sponsor. |
| SRCDOM | Source Data | Req | Name of the parent dataset holding the intercurrent event. Normally the name of the parent SDTM domain. It could also be another ADaM dataset. Include if SRCSEQ is included. |
| SRCSEQ | Source Sequence Number | Req | Sequence number of the intercurrent event record in parent domain. Normally value of --SEQ or of ASEQ if the parent is another ADaM dataset. One of --SEQ or the pair SRCDOM/SRCSEQ is required to point to source record for the intercurrent event. |

**Table 3. ADaM Intercurrent Events Dataset (ADICE) Metadata Specification**

Based on the intercurrent events and handling strategies defined in the Estimand framework, the intercurrent events for the three example subjects should be recorded in the ADICE dataset. Here, ESTzzSTP represents the strategy definition from the Statistical Analysis Plan (SAP), while ESTzzSTA demonstrates the actual implementation based on observed data.

| USUBJID | ASEQ | ATERM | ACAT1 | ASTDT | EST01STP | EST01STA | EST02STP | EST02STA | SRCDOM | SRCSEQ |
|---|---|---|---|---|---|---|---|---|---|---|
| ABC001 | 1 | LUTETIUM-177 | Start new anti-cancer therapy | 2024-11-20 | Hypothetical strategy | | Treatment Policy | Treatment Policy | ADCM | 1 |
| ABC002 | 1 | DOCETAXEL | Start new anti-cancer therapy | 2022-09-30 | Hypothetical strategy | Hypothetical strategy | Treatment Policy | Treatment Policy | ADCM | 2 |
| ABC003 | 1 | Treatment discontinuation | Treatment discontinuation | 2022-11-28 | Treatment Policy | Treatment Policy | Treatment Policy | Treatment Policy | DS | |
| ABC003 | 2 | Radiotherapy | Start new anti-cancer therapy | 2022-11-29 | Hypothetical strategy | Hypothetical strategy | Treatment Policy | Treatment Policy | ADPR | 1 |

**Table 4. ADICE Datasets**

The appropriate strategy for managing intercurrent events (either ESTzzSTP or ESTzzSTA) is determined according to the event occurrence dates, with the specific derivation rules detailed in Table 5.

| Variables | Derivation |
|---|---|
| EST01STP<br>EST01STA | When ACAT1=" Start new anti-cancer therapy":<br>EST01STP="Hypothetical strategy";<br>If F_PD>ASTDT>. or (F_PD=. and ASTDT ne .) then EST01STA="Hypothetical strategy";<br>If .<F_PD<ASTDT then EST01STA="";<br><br>When ACAT1="Treatment discontinuation":<br>EST01STP="Treatment Policy";<br>If ASTDT ne . then EST01STA="Treatment Policy" |
| EST02STP<br>EST02STA | EST02STP="Treatment Policy";<br>If ASTDT ne . then EST02STA=" Treatment Policy";<br>else EST02STA=""; |

**Table 5. Derivation Process**

For records of new anti-cancer therapies in the ADICE dataset, the source domains (SRCDOM) are primarily derived from ADCM (Capture new anti-cancer therapies) and ADPR (Capture subsequent surgeries and radiotherapy). Since start dates may contain partial values, we shall adhere to date imputation rules to complete partial start dates in both CM and PR domains before generating the corresponding ADCM and ADPR datasets, which are then consolidated into ADICE.

Key Implementation Process:

1. Source Data Handling:
   - Original records are extracted from SDTM CM (Concomitant Medications) and PR (Procedures) domains
2. ADaM Transformation:
   - Date-imputed CM/PR data are processed into corresponding ADaM datasets (ADCM/ADPR)
3. ADICE Integration:
   - Final records are consolidated into ADICE after ADCM and ADPR derivation
   - Ensures traceability through:
     - SRCDOM = "ADCM" or "ADPR" or "DS"
     - SRCSEQ = Source record sequence number

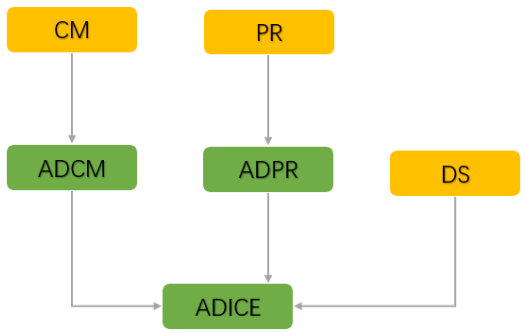


**Figure 2. Data Flow to ADICE**

## CONSIDERATIONS FOR GENERATING ADTTE

The above section details the processing of the Intercurrent Events dataset. For the analysis of the Time to Event Analysis Dataset, additional censoring rules need be accounted for. It is recommended to first finalize the Intercurrent Events dataset. Subsequently, when preparing the ADTTE (Time to Event Analysis Dataset) for efficacy endpoints, all relevant censoring rules need to be comprehensively incorporated into the analysis.

## CONCLUSION

Prior to the implementation of ICH E9(R1), oncology studies using time-to-event endpoints also censored subsequent anti-cancer therapies, meaning efficacy assessments after the initiation of new anti-cancer treatments were excluded—similar to applying a hypothetical strategy for new anti-cancer therapies in the estimand framework. In sensitivity analyses, efficacy assessments following the start of new anti-cancer therapies were included, analogous to applying a treatment policy strategy for new anti-cancer therapies in the estimand framework.

In accordance with the requirements of ICH E9(R1), it is necessary to summarize and report the number and timing of various intercurrent events by treatment group. Organizing an intercurrent event dataset facilitates the generation of summary tables for these events. Therefore, creating the ADICE dataset is essential. In oncology clinical trials utilizing Time-to-Event as efficacy endpoints, since subsequent lines of anti-cancer treatment can potentially affect endpoint assessment, it is recommended to include only the first occurrence of new anti-cancer therapy in the intercurrent events dataset.

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## ACKNOWLEDGMENTS

I would like to express my sincere gratitude to my supervisors Wenjun Zhu and Yi Yang for their expert guidance and constructive suggestions. My thanks also go to my colleagues—Huating Shang, Wenze Li, Qiuxing Chen and Xiaojuan Li—for providing valuable project references and factual evidence.

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