Estimands for Overall Survival with Treatment Switching in Oncology Clinical Trials

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On behalf of the **Pharmaceutical Industry Working Group on "Estimands in Oncology"** (www.oncoestimand.org) sponsored by PSI and EFSPI and ASA scientific working group of the ASA biopharmaceutical section.

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Oncology Estimands Working Group

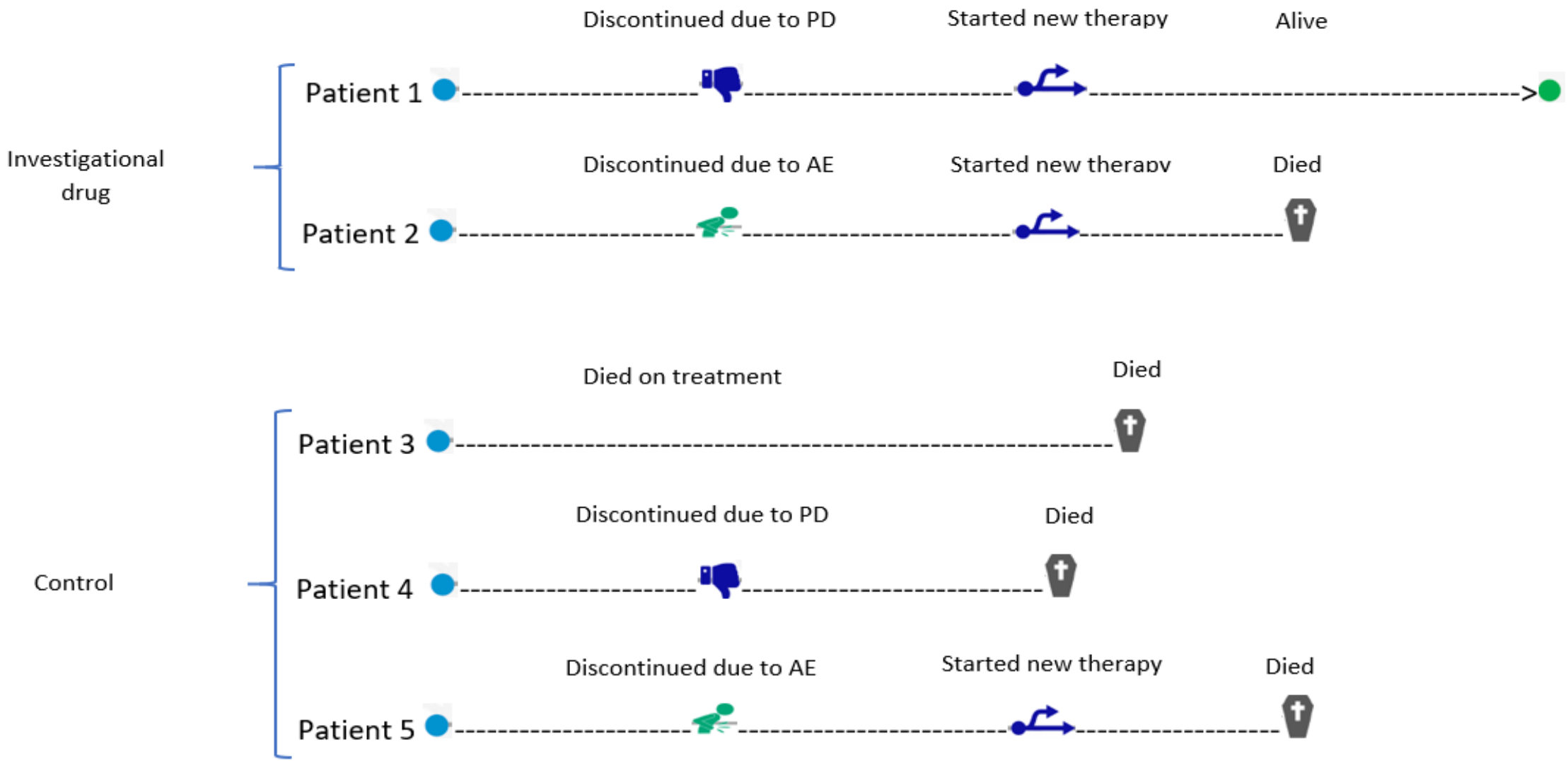
- initiated and led by Evgeny Degtyarev (Novartis) and Kaspar Rufibach (Roche), first TC Feb 2018
- **EFSPI Special Interest Group** (Nov 2018) and **ASA Biopharm Section Scientific Working Group** (Apr 2019)
- as of 19-Apr-2023 WG has 99 members (37 from Europe, 52 from US, and 10 from Asia) epresenting **48** companies
- Goal: **A common understanding and consistent implementation across industry** in dialogue with regulators from EMA, FDA, Japan, China, Taiwan, Canada, MHRA
- **Weblink** www.oncoestimand.org.

Introduction

- The need for the **Addendum on Estimands and Sensitivity Analysis in Clinical Trials E9 (R1)** was identified due to recurrent issues with a lack of clarity in trial objectives and related treatment effect of interest.

- In November 2019, the International Conference for Harmonization of Technical Requirements for Pharmaceuticals for Human Use released an Addendum to E9 guideline on Statistical Principles for Clinical Trials that:
  - Introduced structured framework for clinical trial design
  - Defined intercurrent events, which occur after treatment initiation and affect either the existence or interpretation of the measurement
  - Highlighted the difficulty of assessing treatment effect in the presence of intercurrent events

Potential Journeys of Cancer Patients in Clinical Trials



Potential Journeys of Cancer Patients in Clinical Trials

- Can the prolonged survival be attributed to the investigational drug?

  or
- Is it the effect of subsequent therapy?

  or
- What would have been the survival of patients one and two had they not received the new therapies?

- What is the **key question of interest**:
  - Overall Survival (OS), irrespective of another therapy?

  or
  - Overall Survival, had patients not received new therapies?

Treatment Switching

- Per E9(R1), subsequent therapy is an intercurrent event
- In oncology, the start of new therapy after study treatment discontinuation or treatment switching is a **key intercurrent event**

Description of Treatment Switching	**Type of Treatment Switching**
From control arm to investigational arm	Crossover
From control arm to same drug class as investigational arm	Treatment switching
From control or investigational arm to a drug (class) of interest	Treatment switching

Strategies to Handle Start of New Therapy

- **Treatment policy strategy question of interest:** Survival benefit of investigational drug irrespective of what happens after treatment discontinuation
  - It is assumed that subsequent therapies given after treatment discontinuation reflect clinical practice
  - This strategy corresponds to the ITT approach
  - Might be not always a meaningful strategy

- **Hypothetical strategy question of interest:** Survival benefit of investigational drug in the hypothetical scenario in which patients do not receive subsequent therapies, i.e. adjusted for the effect of subsequent therapies
  - Often used as supportive post-hoc analysis in oncology trials after observing treatment policy may not be addressing the clinical question of interest

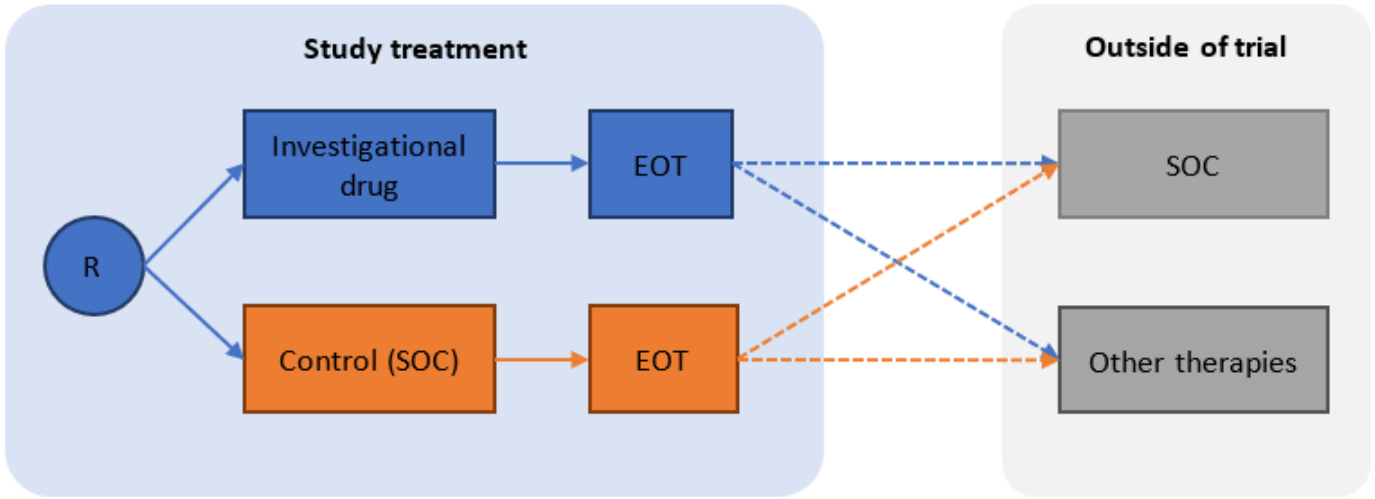
Current Practice. Motivation

- Traditional analysis of OS in the confirmatory study is performed ignoring treatment switching (treatment policy)

- Survival benefit of investigational treatment is likely to be underestimated when control group patients switch more frequently to a treatment prolonging OS

Treatment Switching Scenario 1

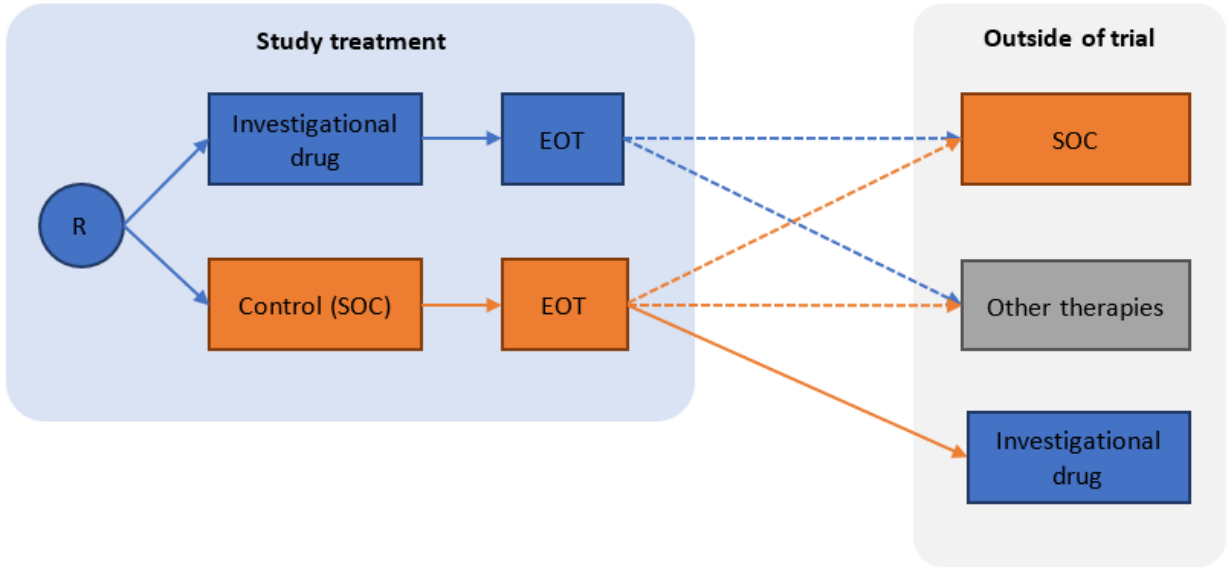
- Investigational drug vs. control; both arms can receive subsequent therapies reflecting clinical practice



Clinical question of interest:
What is the OS benefit of the investigational drug vs. Standard of Care (SOC) irrespective of subsequent therapies? => Treatment policy strategy
The comparison is between the sequence of investigational drug and other therapies and the sequence of control treatment and other therapies

Treatment Switching Scenario 2

- Investigational drug vs. control; investigational drug is approved as next-line therapy after SOC



- **Clinical question of interest 1:**

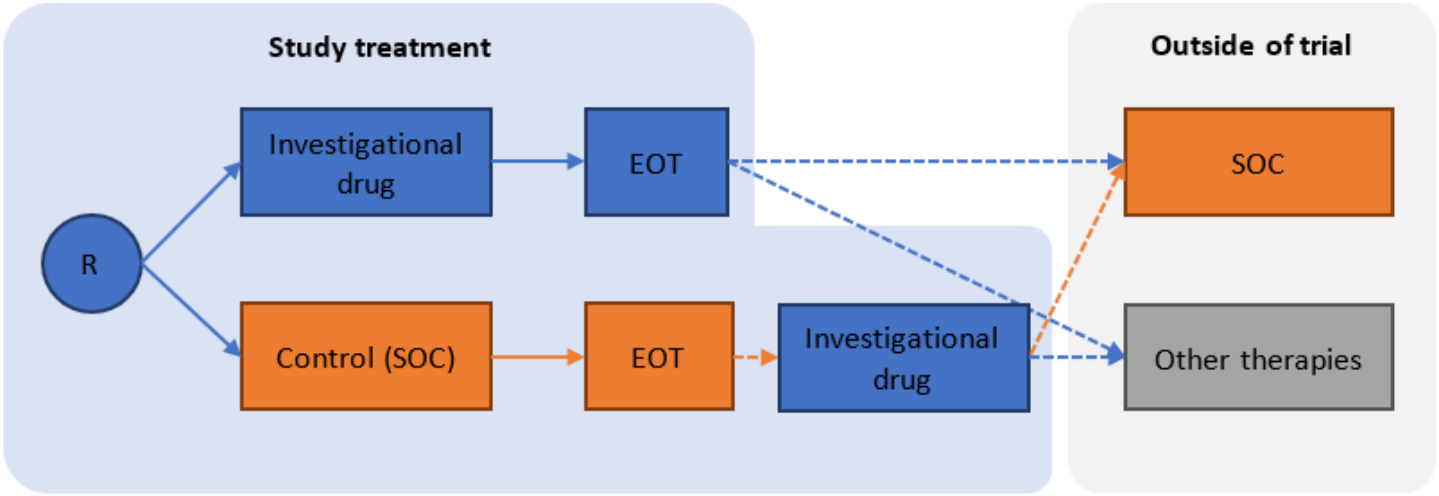
What is the OS benefit of the investigational drug vs. SOC irrespective of subsequent therapies? => Treatment policy strategy, SOC represents sequence of control treatment and investigational drug

- **Clinical question of interest 2:**

What is the OS benefit of the investigational drug vs. SOC had patients not switched to other therapies? => Hypothetical strategy, comparison between investigational drug and SOC

Treatment Switching Scenario 3

- Investigational drug vs. control with crossover to not yet approved investigational drug



Clinical question of interest:
What is the OS benefit of the investigational drug vs. SOC if crossover opportunity does not exist? =>
Hypothetical strategy could be more informative for clinicians and patients

Estimands in the Presence of Treatment Switching

Objective		Evaluate OS benefit under the assumption switching is not associated with survival/covariates.	Evaluate OS benefit adjusted for treatment switching	Evaluate OS benefit adjusted for treatment crossover	Evaluate OS benefit adjusted for treatment crossover at disease-related time-point
Population		Defined through appropriate I/E criteria to reflect the target patient population for approval			
Variable		Overall survival: Time from randomization to death			
Treatment condition of interest		Sequence of Investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapies (including investigational drug)	Investigational drug vs control	Investigational drug vs sequence of control + other subsequent therapy	Investigational drug vs control
Handling of intercurrent events	Start of subsequent therapy	Treatment policy	Hypothetical	Hypothetical	Hypothetical
	Crossover	Treatment policy	Hypothetical	Hypothetical	Hypothetical
Population-level Summary		ITT analysis: Cox model and KM estimates;	IPCW estimates: Adjusted HR and CI from IPCW-weighted Cox model; weighted KM estimates	RPSFT / IPCW estimates: HR based on adjusted survival times from Cox model / parametric survival model, bootstrap CI for test decision.	Two-stage (IPCW /RPSFT) method: Estimate HR using reconstructed survival;

Conclusions and Summary

- Standard practice should account for treatment switching in the analysis during the planning stage of the trial to incorporate that into design and data collection strategies.
- Estimand, where treatment switching is handled with treatment policy, is meaningful in most situations and is appropriate only if subsequent therapies reflect clinical practice.
- In situations, when subsequent therapies are not clinical practice, other estimands handling treatment switching with hypothetical strategy are more versatile.
- Construct appropriate estimand to answer pre-specified scientific question of interest

Further reading: Corresponding manuscript published in Pharmaceutical Statistics (DOI: 10.1002/pst.2158)

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MAIN PAPER

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Estimands for overall survival in clinical trials with treatment switching in oncology

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Abstract

An addendum of the ICH E9 guideline on Statistical Principles for Clinical Trials was released in November 2019 introducing the estimand framework. This new framework aims to align trial objectives and statistical analyses by requiring a precise definition of the inferential quantity of interest, that is, the estimand. This definition explicitly accounts for intercurrent events, such as switching to new anticancer therapies for the analysis of overall survival (OS), the gold standard in oncology. Traditionally, OS in confirmatory studies is analyzed using the intention-to-treat (ITT) approach comparing treatment groups as they were initially randomized regardless of whether treatment switching occurred and regardless of any subsequent therapy (treatment-policy strategy). Regulatory authorities and other stakeholders often consider ITT results as most relevant. However, the respective estimand only yields a clinically meaningful comparison of two treatment arms if subsequent therapies are already approved and reflect clinical practice. We illustrate different scenarios where subsequent therapies are not yet approved drugs and thus do not reflect clinical practice. In such situations the hypothetical strategy could be more meaningful from patient's and prescriber's perspective. The cross-industry Oncology Estimand Working Group (www.oncoestimand.org) was initiated to foster a common understanding and consistent implementation of the estimand framework in oncology clinical trials. This paper summarizes the group's recommendations for appropriate estimands in the presence of treatment switching, one of the key intercurrent events in oncology clinical trials. We also discuss how different choices of estimands may impact study design, data collection, trial conduct, analysis, and interpretation.

KEYWORDS

cross-over, estimand, ITT, overall survival, treatment switching

On behalf of the European special interest group "Estimands in oncology," sponsored by PSI and EPSPI and ASA scientific working group of the ASA biopharmaceutical section