Estimands for Overall Survival in Clinical Trials with Treatment Switching in Oncology

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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.

Oncology Estimands WG

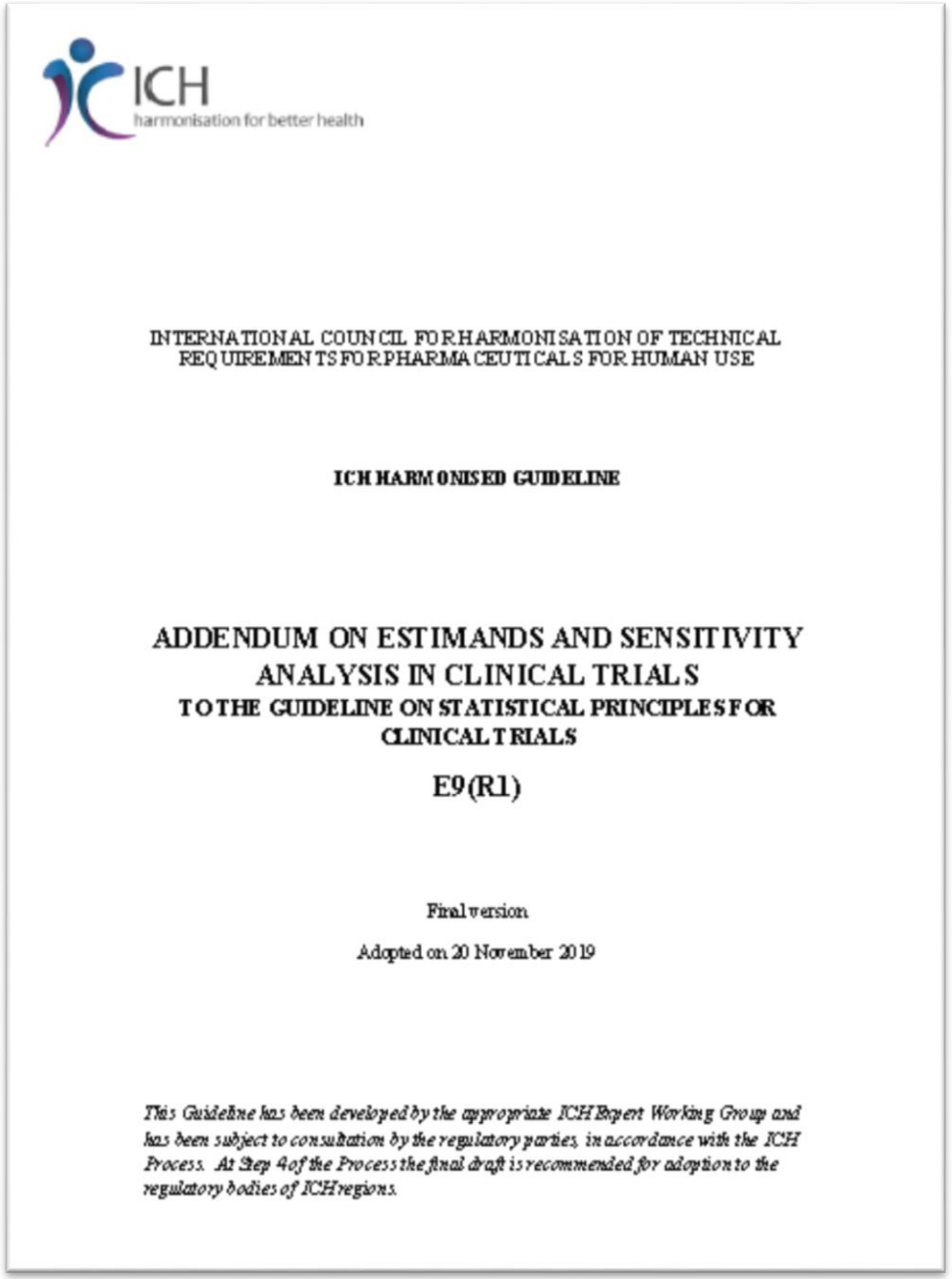
- initiated and led by Evgeny Degtyarev (Novartis) and Kaspar Rufibach (Roche), first TC Feb 2018
- **EFSPI Special Interest Group** (Nov 2018) and **ASA Biopharm Section Scientific Working Group** (Apr 2019)
- Large number of members from Europe and US representing **24** companies
- Goal: **A common understanding and consistent implementation across industry** in dialogue with regulators from EMA, FDA, Japan, China, Taiwan, Canada, MHRA
- **Weblink** www.oncoestimand.org.

Background

ICH E9(R1) guideline introduced the estimand framework in November 2019

Aim:

- Increase transparency with respect to data analysis and inference
- Align trial objectives and statistical analyses by requiring a precise definition of the population quantity of interest
- Strengthen the dialogues between disciplines involved in the formulation of clinical study objectives, design, conduct, analysis and interpretation



ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS
TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9(R1)

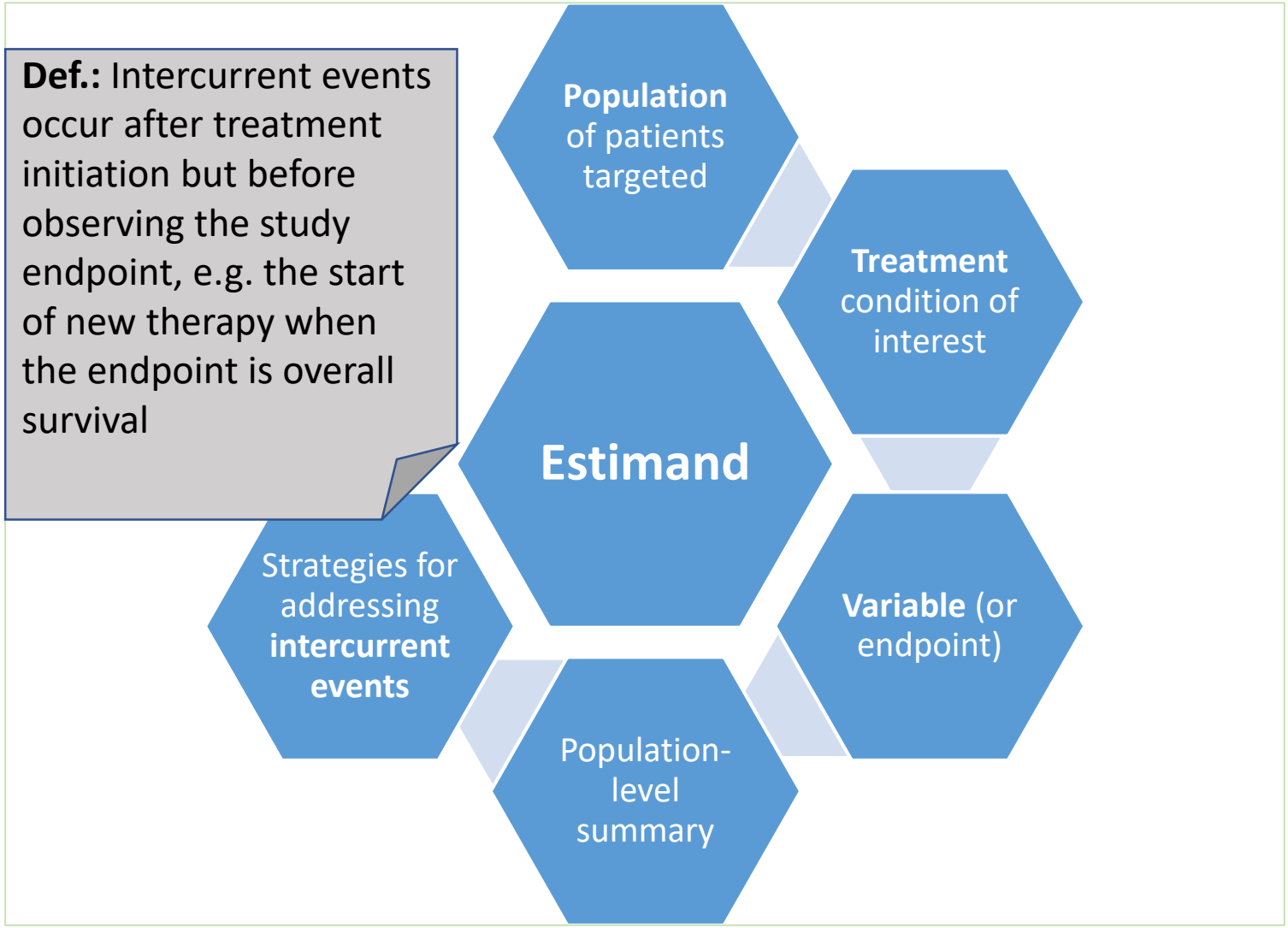
Final version

Adopted on 20 November 2019

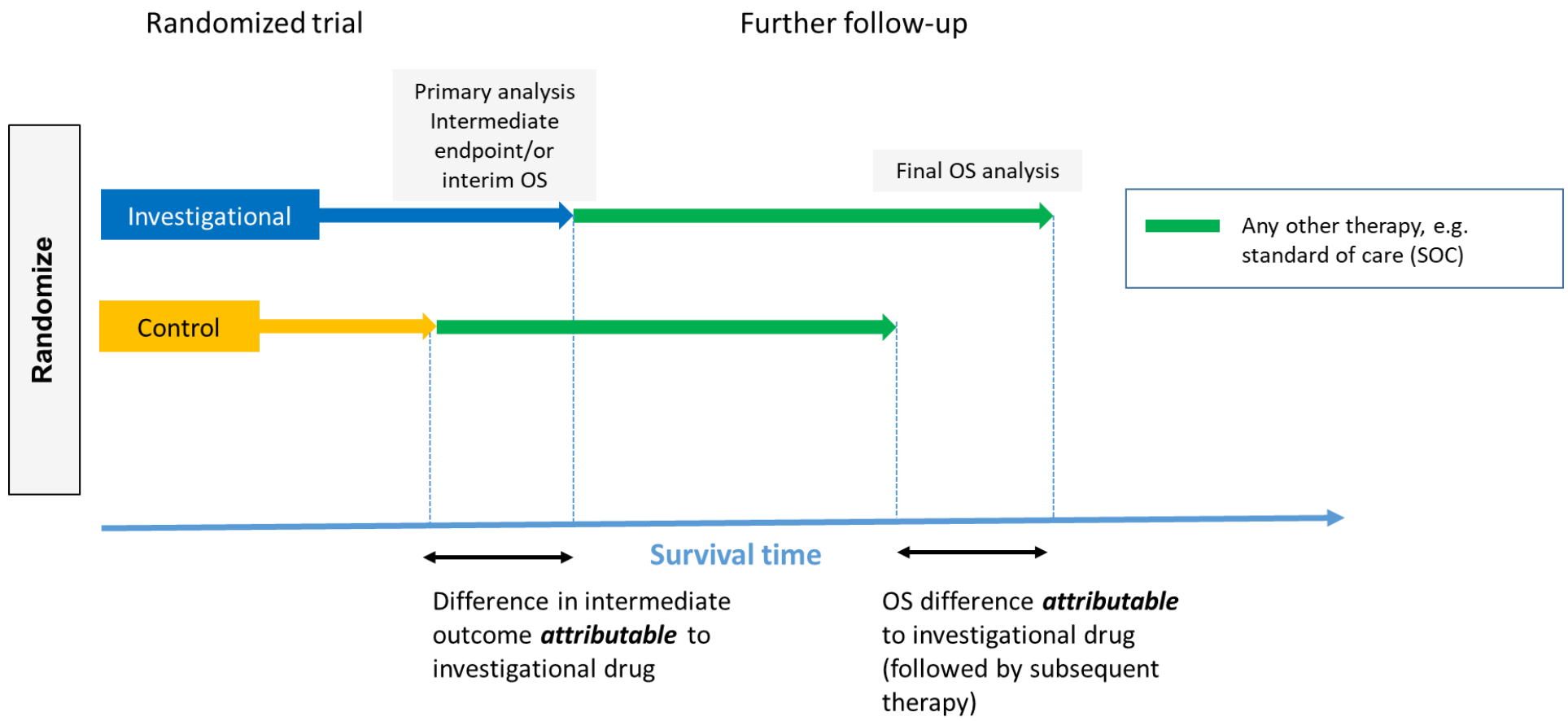
This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

What is an Estimand?

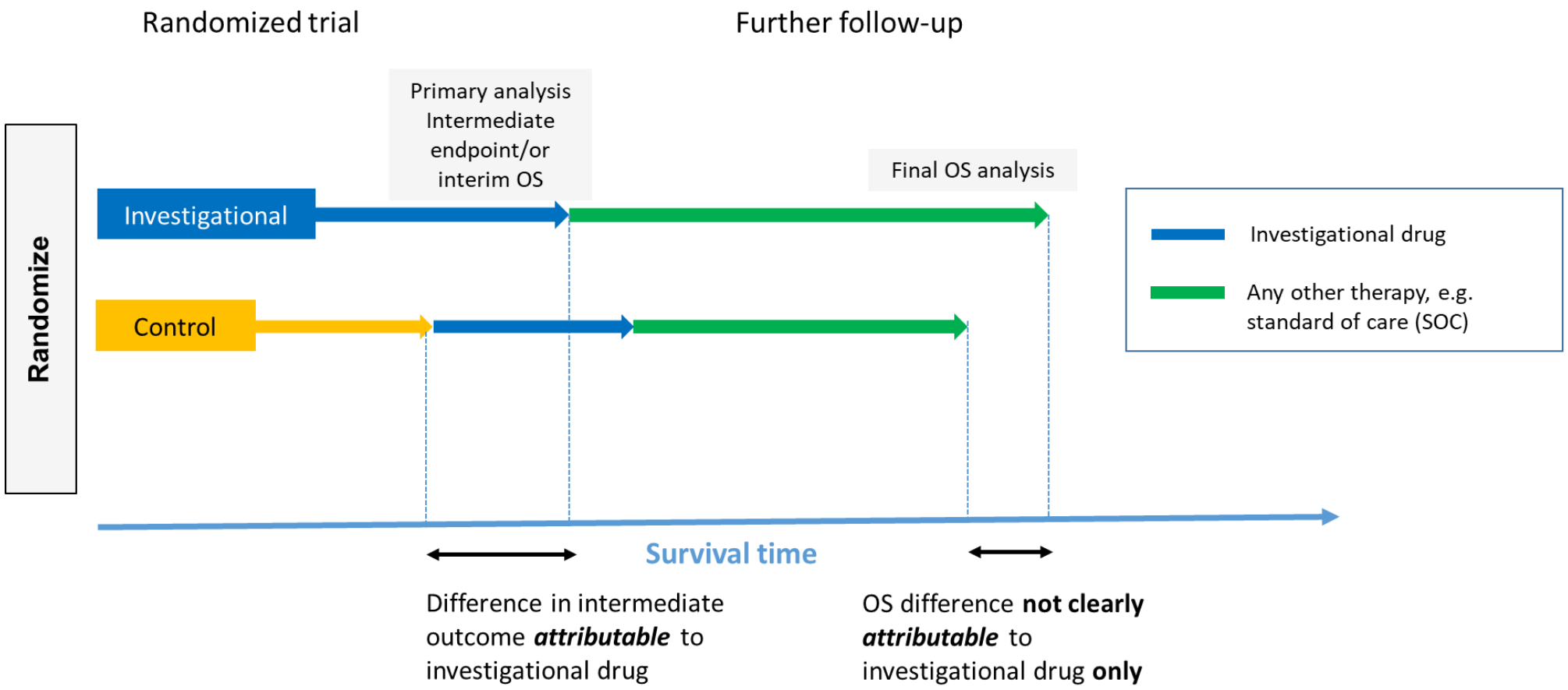
- **Estimand** is the target of estimation to address the scientific question of interest posed by the study objective.
- An estimand is described by five attributes, defining together the treatment effect of interest.
- This definition explicitly accounts for intercurrent events, such as switching to new anticancer therapies for the analysis of overall survival (OS), the gold standard in oncology.



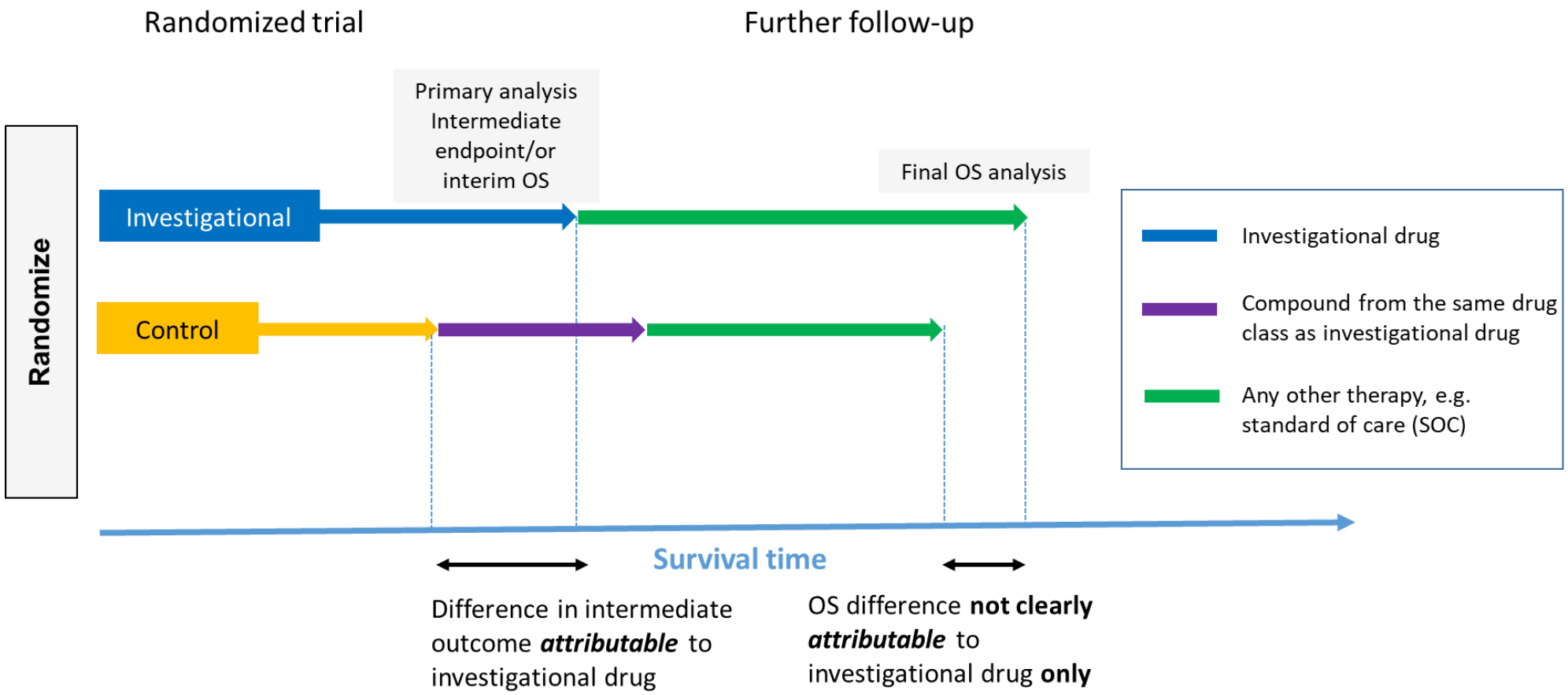
Randomized Clinical Trial in Oncology:
A Stylized Example



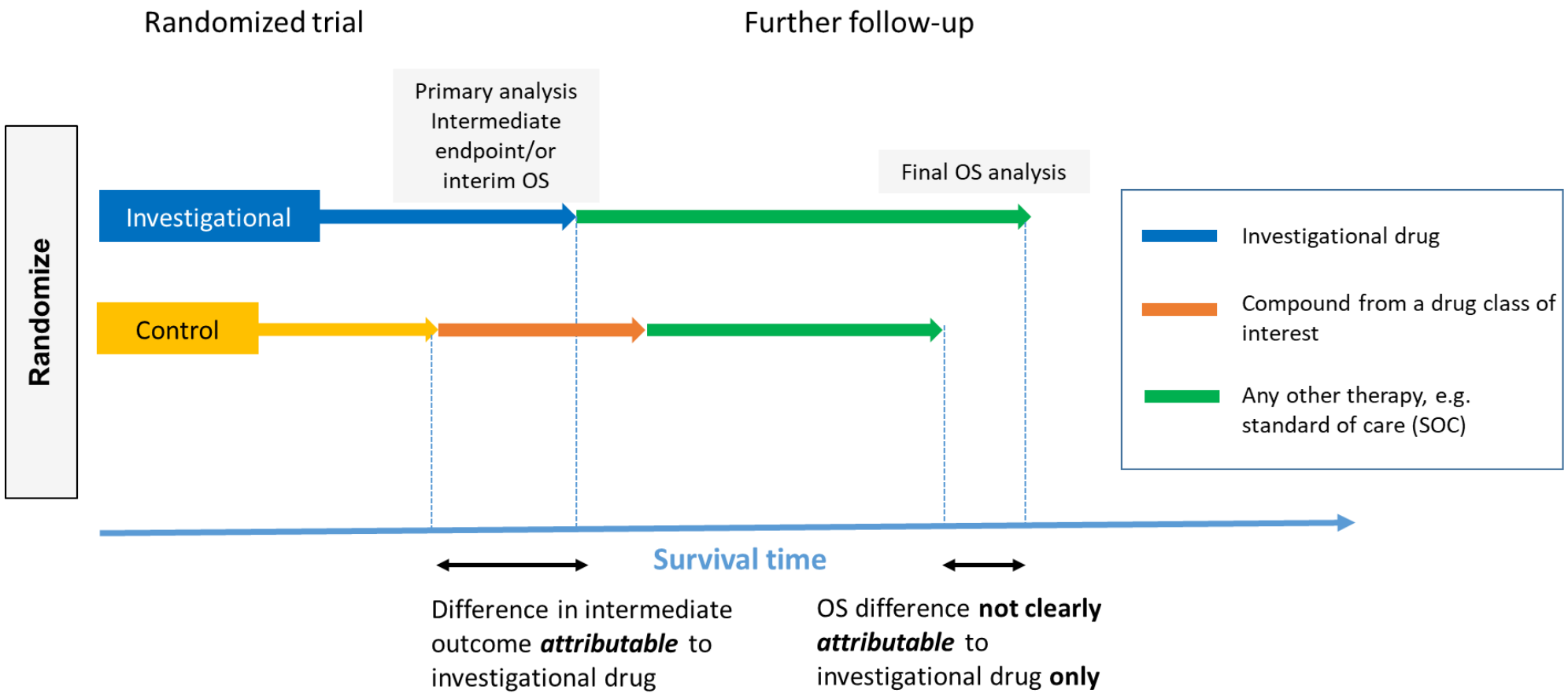
Treatment Switching Scenario 1:
Cross-over from Control to Investigational Arm



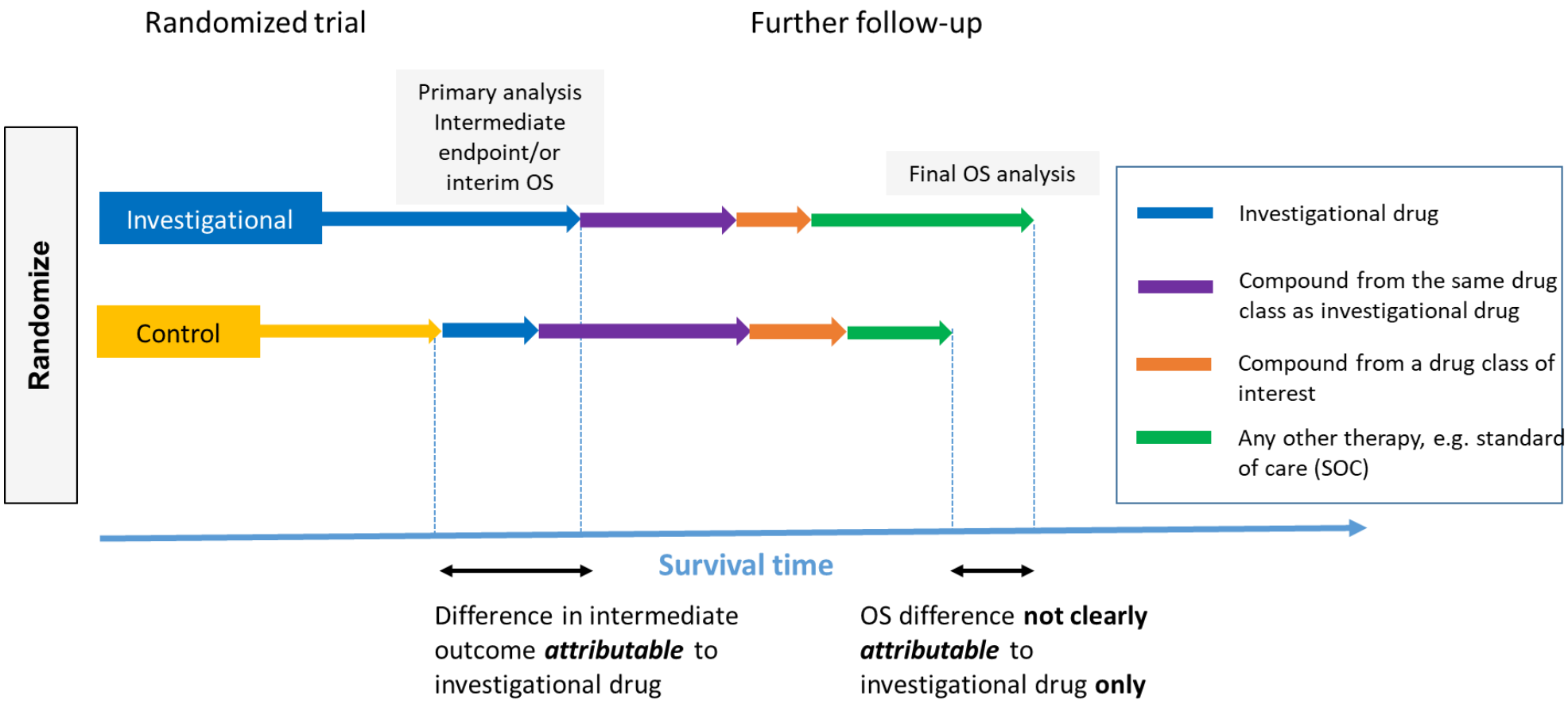
Treatment Switching Scenario 2:
From Control to Same Drug Class as of Investigational Arm



Treatment Switching Scenario 3:
From Control Arm to Drug Class of Interest



A More Realistic Example:
Mix of Treatment Switching Scenarios



What do we actually measure? What are the key questions?

- The traditional approach ignores treatment switching and rest on the following assumptions:
  - ✓Subsequent therapy reflect clinical practice (including investigational drug in later line) **in particular decision context**
  - ✓Patients receiving subsequent treatments (from same class as investigational drug and drug class of interest) and dose intensity as expected (as SOC) between investigational and control arm
- If these assumptions do not hold, we may consider to estimate the OS benefit that is attributable to the investigational drug
- The estimand framework provides a coherent framework to make the arising issues of treatment switching explicit and offers a systematic and transparent approach for assessment

Treatment Policy Strategy for Treatment Switching

- ***Objective:*** Evaluate OS benefit assuming subsequent therapies represent clinical practice
- ***Estimand:***
  - **Population:** Defined through appropriate I/E criteria to reflect the target patient population for approval
  - **Variable:** Overall survival, defined as the time from randomization to death
  - **Treatment:** Sequence of investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapies (including Investigational drug)
  - **Handling of intercurrent events:**
    - Start of subsequent therapy at any time: Treatment policy
    - Crossover to investigational drug at any time: Treatment policy
    - Crossover to investigational drug at disease progression: Treatment policy
  - **Population-level Summary:** Hazard ratio and confidence interval
- ***Estimate:*** Cox model and KM estimates using ITT approach

Hypothetical Strategy for Treatment Switching

- ***Objective:*** Evaluate OS benefit adjusted for treatment switching
- ***Estimand:***
  - **Population:** Defined through appropriate I/E criteria to reflect the target patient population for approval
  - **Variable:** Overall survival, defined as the time from randomization to death
  - **Treatment:** Investigational drug vs control (if there were no subsequent therapies)
  - **Handling of intercurrent events:**
    - Start of subsequent therapy at any time: Hypothetical
    - Crossover to investigational drug at any time: Hypothetical
    - Crossover to investigational drug at disease progression: Hypothetical
  - **Population-level Summary:** Hazard ratio and confidence interval
- ***Estimate:*** Adjusted HR and CI from IPCW-weighted Cox model

Estimands in Clinical Trials with Treatment Switching

OBJECTIVE	*Evaluate OS benefit assuming subsequent therapies represent clinical practice*	*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*
ESTIMAND				
Population	Defined through appropriate I/E criteria to reflect the target patient population for approval			
Variable / Endpoint	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 (if there were no subsequent therapies)	Sequence of investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapy (excluding investigational drug)	Sequence of Investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapy (excluding investigational drug)
Handling of intercurrent events (IEs)				
IE: Start of subsequent therapy at any time	Treatment policy	Hypothetical	Treatment policy	Treatment policy
IE: Crossover to investigational drug at any time	Treatment policy	Hypothetical	Hypothetical	Treatment policy
IE: Crossover to investigational drug at disease progression	Treatment policy	Hypothetical	Hypothetical	Hypothetical
Population-level Summary	Kaplan – Meier estimates; Hazard ratio (HR) with confidence interval (CI)			
ESTIMATION	Cox model and KM estimates using ITT approach	Adjusted HR and CI from IPCW-weighted Cox model; weighted KM estimates	HR from RPSFT model using adjusted survival times; IPCW methods could also be used	HR from two-stage method using reconstructed survival; IPCW and RPSFT methods could be used

Conclusions & Summary

- Treatment policy estimand may not be clinically relevant if subsequent therapy does not represent clinical practice
- The estimand framework provides a coherent framework to make the issues of treatment switching explicit and offers a systematic and transparent approach for assessment
- Start to think about possible treatment switching scenarios during the planning phase of a trial
- Choose appropriate estimand according to pre-specified scientific question of interest
- Treatment switching methods which can be applied if the necessary data is collected; assumptions apply

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 EFSPI and ASA scientific working group of the ASA biopharmaceutical section

