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Organizational Announcements

- Please use the Q&A functionality from Zoom to raise questions throughout the presentation.
- Please use the Chat functionality from Zoom for technical issues.

International Oncology Estimands Working Group

- Goal: A common understanding across industry
- As of 13 April 2021, the working group has 61 members (from Europe, US, and Asia) representing 33 companies
- EFSPI SIG (Nov 2018) and ASA Biopharm Section SWG (Apr 2019)
- In dialogue with eight health authorities globally
- Weblink www.oncoestimand.org

Engagement Working Group

	**Stefan Englert** has 9+ years of experience in oncology drug development working for AbbVie Germany and **leads the clinical engagement task force** of the cross-industry international working group on estimands in oncology. **Moderator of this session.**	abbvie
	**Paul Bycott** has 24 years of pharmaceutical experience predominately in oncology. He is currently the Head of the Breast Cancer Franchise for statistics at Pfizer. **Co-Presenter.**	Pfizer
	**Feng Liu** has 20+ years of experience in pharmaceutical drug development working for Intercept Pharma. **Co-Presenter.**	Intracept
	**Rui (Sammi) Tang** is the VP Global Biometric Head Oncology at Servier Pharmaceuticals US. **Co-Presenter.**	SERVIER
	**Jiawei Wei** is currently a Director Statistical Consultant in the Advanced Methodology and Data Science group at Novartis.	NOVARTIS
	**Jonathan Siegel** is Director of Oncology Clinical Statistics US at Bayer with over 20 years' experience in pharmaceutical oncology in multiple companies.	BAYER

Learning Outcomes

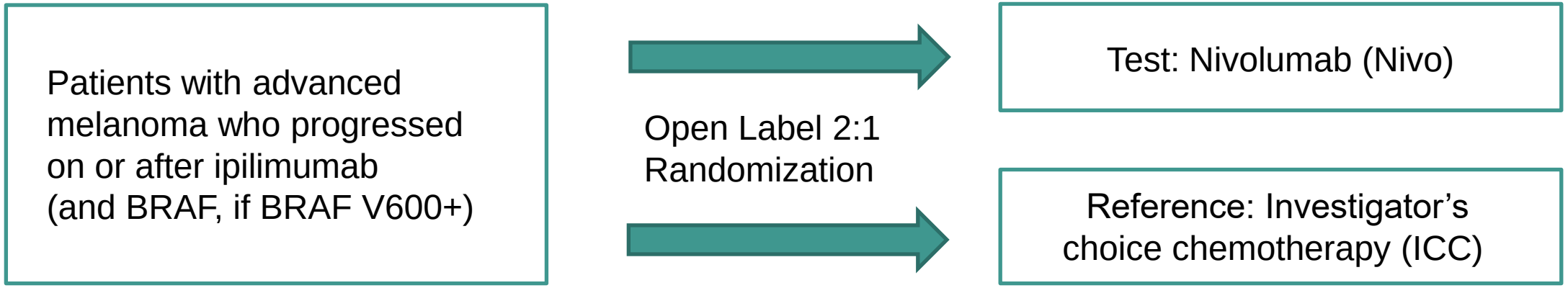
- **Recognize the benefits** of following the estimand framework (ICH E9 (R1) addendum) in the context of a clinical trial, in order to:
  - have a common language to describe the diversity of patient journeys
  - address the right question in clinical trials
- **Be able to construct an estimand**, including identification of relevant intercurrent events and application of relevant strategies to address them
- **Gain insights** from a cross-industry international working group and a panel of leading experts on estimands in oncology

Agenda

Introductions, Acknowledgements and Learning Outcomes	Stefan Englert (AbbVie)
Introduction to the case study	Paul Bycott (Pfizer)
Intermezzo	Feng Liu and Sammi Tang (Servier)
Estimands in Oncology – How and Why	Feng
Revisiting the case study	Paul
Interactive Quiz with Q&A • Quiz to the audience • Panel Discussion	Sammi
Concluding Remark	Stefan

Motivating Example: Checkmate-37

Nivolumab (an immune checkpoint inhibitor) versus chemotherapy in patients with advanced melanoma who progressed after ipilimumab treatment: a randomized, controlled, open-label, phase 3 trial.



Primary Objectives

- To show superiority in overall survival (OS) of nivolumab over chemotherapy
- To estimate the objective response rate (ORR) in the nivolumab treatment group (noncomparative assessment)

Reference: Lancet Oncology. 2015 Apr;16(4):375-84. doi: 10.1016/S1470-2045(15)70076-8.

Checkmate-37

Overall Survival (OS)

Defined as the time from randomization until death from any cause.

Survival is considered the most reliable cancer endpoint and is usually the preferred endpoint.

Objective Response Rate (ORR)

Defined as the proportion of subjects who had achieved an objective response. Used as an early indicator of activity.

Best Overall Response	Description
Complete Response (CR)	Disappearance of all disease
Partial Response (PR)	At least a 30% decrease in tumor burden from baseline
Stable Disease (SD)	None of the others
Progressive Disease (PD)	New disease or at least 20 % increase in tumor burden from nadir

Objective Response

Note: Simplified presentation for patients without non-target lesions.

Reference: RECIST 1.1. European Journal of Cancer 45 (2009) 228-247

Checkmate-37: Early assessment of ORR

- **31.7% ORR in Nivolumab group (n=120)**
  - 95% CI: (23.5,40.8) excludes pre-defined 15% threshold
- 10.6% ORR in investigator's choice chemotherapy group (n=47)
  - 95% CI: (3.5,23.1)

Accelerated approval for Nivolumab granted in USA

- Based on ORR data
- Confirmatory evidence expected from this or other trials

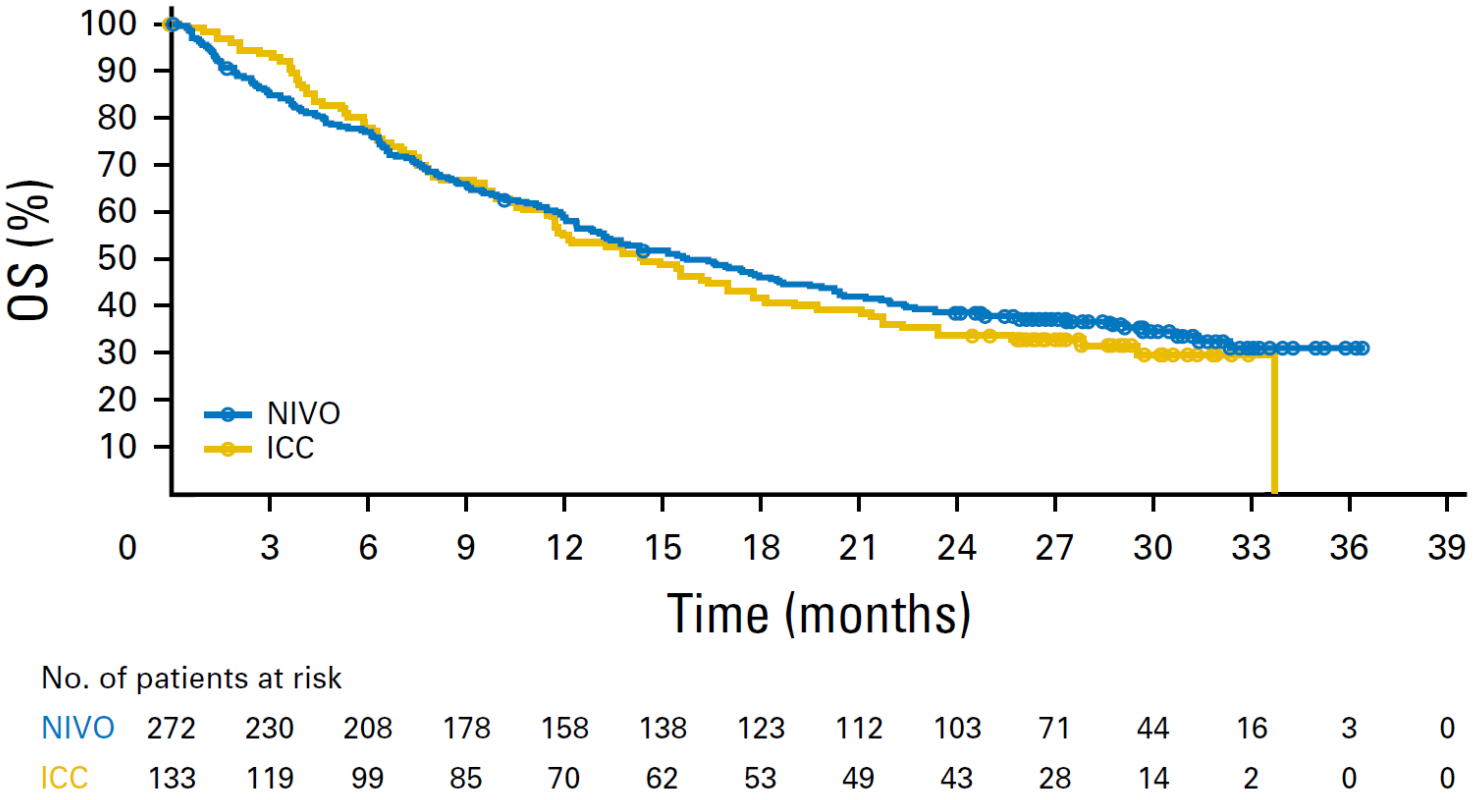
Full approvals for Nivolumab granted in USA, EU and Japan

- Based on additional readouts from other trials
- Prior to overall survival analysis

Study continued until primary analysis of overall survival

Checkmate-37: Final assessment of Overall Survival

Overall survival: Hazard Ratio = 0.95, median overall survival 15.7 months vs 14.4 months



No. of patients at risk

NIVO	272	230	208	178	158	138	123	112	103	71	44	16	3	0
ICC	133	119	99	85	70	62	53	49	43	28	14	2	0	0

CheckMate 037: Nivolumab Improved Responses, Not Survival in Advanced Melanoma

July 17, 2017

Leah Lawrence

Reference: https://www.cancernetwork.com/view/checkmate-037-nivolumab-improved-responses-not-survival-advanced-melanoma (red highlight added)

Reference: Journal of Clinical Oncology 36, no. 4 (February 01, 2018) 383-390. doi: 10.1200/JCO.2016.71.8023

Impact on Industry Reputation

PHARMALOT

STAT+

Flawed trials supported half of recent approvals of cancer drugs in Europe, study says

By ED SILVERMAN @Pharmalot / SEPTEMBER 18, 2019

ELSEVIER

Journal of Clinical Epidemiology

Volume 127, November 2020, Pages 1-8

Original Article

Evidence of survival benefit was often ambiguous in randomized trials of cancer treatments

THE MILBANK QUARTERLY

A MULTIDISCIPLINARY JOURNAL OF POPULATION HEALTH AND HEALTH POLICY

Original Scholarship | Open Access

Approval of Cancer Drugs With Uncertain Therapeutic Value: A Comparison of Regulatory Decisions in Europe and the United States

MAXIMILIAN SALCHER-KONRAD, HUSEYIN NACI, COURTNEY DAVIS

First published: 06 October 2020 | https://doi.org/10.1111/1468-0009.12476

Conclusions: US and European regulators often deemed early and less complete evidence on benefit-risk profiles of cancer drugs sufficient to grant regular approval, raising questions over regulatory standards for the approval of new medicines. Even when imposing confirmatory studies in the postmarket-

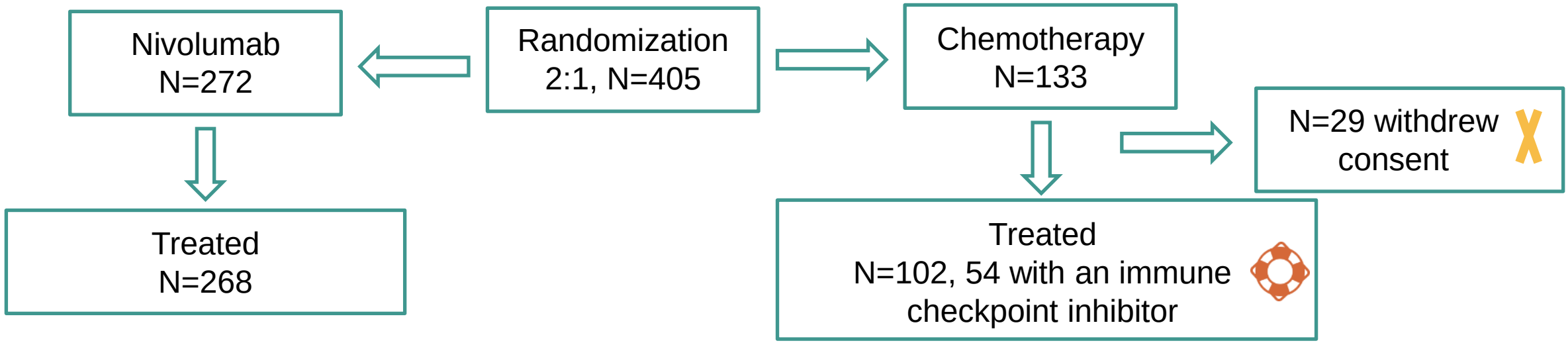
The Guardian International edition

Over half of new cancer drugs 'show no benefits' for survival or wellbeing

Of 48 cancer drugs approved between 2009-2013, 57% of uses showed no benefits and some benefits were 'clinically meaningless', says BMJ study

Checkmate-37: Patient Flow Chart

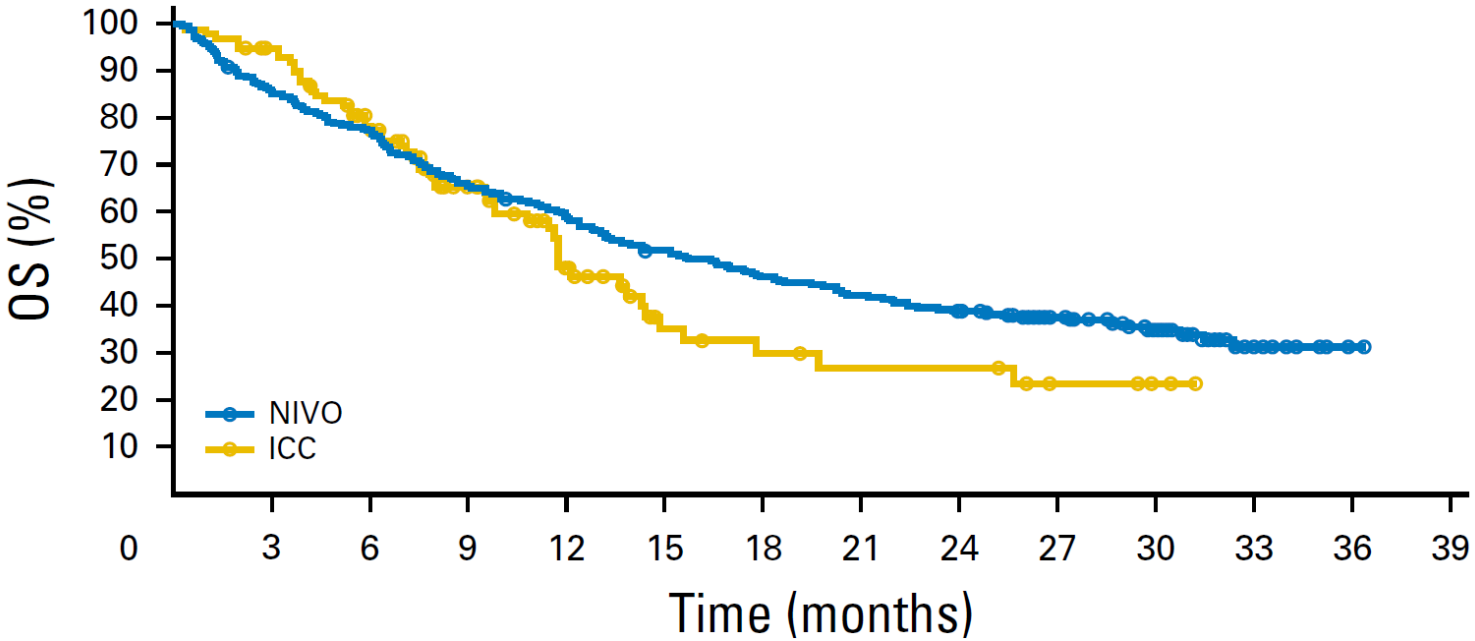
Open-label trial and several competing studies with other checkpoint inhibitors ongoing at the time of enrollment



Observation	
Patient opted out of prescribed treatment	Pre-treatment: 22% in chemotherapy-arm withdrew consent immediately after randomization
Checkpoint inhibitor therapy received (drug from same class)	Post-treatment discontinuation: at least 41% in chemotherapy-arm received another checkpoint inhibitor

Post-hoc analysis of overall survival

Overall survival in **treated** patients with subjects **censored if they start another check point inhibitor treatment**: Hazard Ratio = 0.81, median OS: 16.4 months vs 11.8 months



No. of patients at risk

NIVO	268	229	207	177	157	137	122	112	103	71	44	16	3	0
ICC	102	94	73	48	28	14	11	9	9	5	2	0	0	0

CheckMate 037: Nivolumab Improved Responses, Not Survival in Advanced Melanoma

?

July 17, 2017

Leah Lawrence

Reference: https://www.cancernetwork.com/view/checkmate-037-nivolumab-improved-responses-not-survival-advanced-melanoma (red highlight added)

Highlighting the importance to address the right question in clinical trials

Reference: Journal of Clinical Oncology 36, no. 4 (February 01, 2018) 383-390. doi: 10.1200/JCO.2016.71.8023

This is a great example ..., but I think the issue in Checkmate is not necessarily what is seen in a typical study...

Our clinical trial is aligned to agreed objectives!

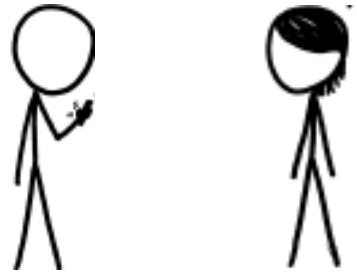
So, show me your meaningful description of the treatment effect?

1

That's easy. Objectives are in Section 3 of the protocol.

Endpoints are defined later.

The handling of special events is described somewhere in the Statistical Analysis Plan. At least that is my understanding.



2

After you put all these pieces together you will know what we actually wanted .

Even if not, we are able to perform additional analyses to fulfill all needs. Well, as long as we have collected the appropriate data to do so...

Are you sure your study team, your management, and regulators always come to the same conclusion?

Seems like a lot of additional work

3

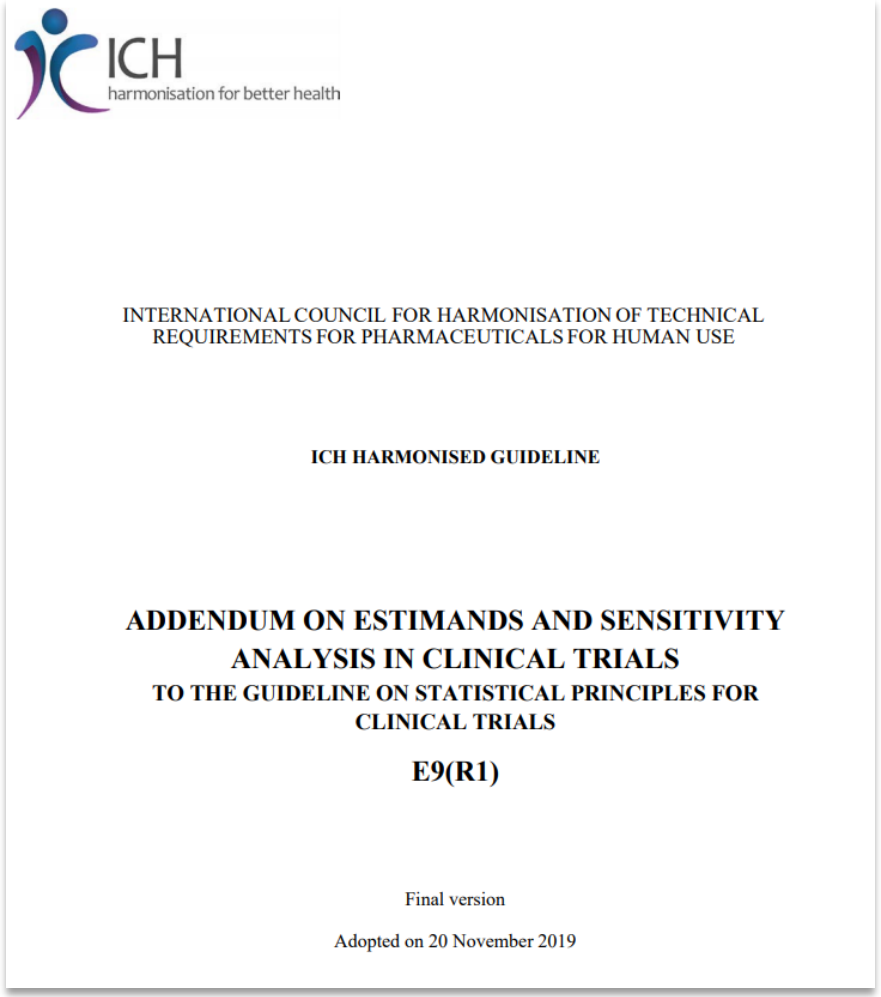
Fair enough. If only we had a structured framework that fully aligns the trial with the clinical objectives...

It's already here! It's called the Estimand Framework.

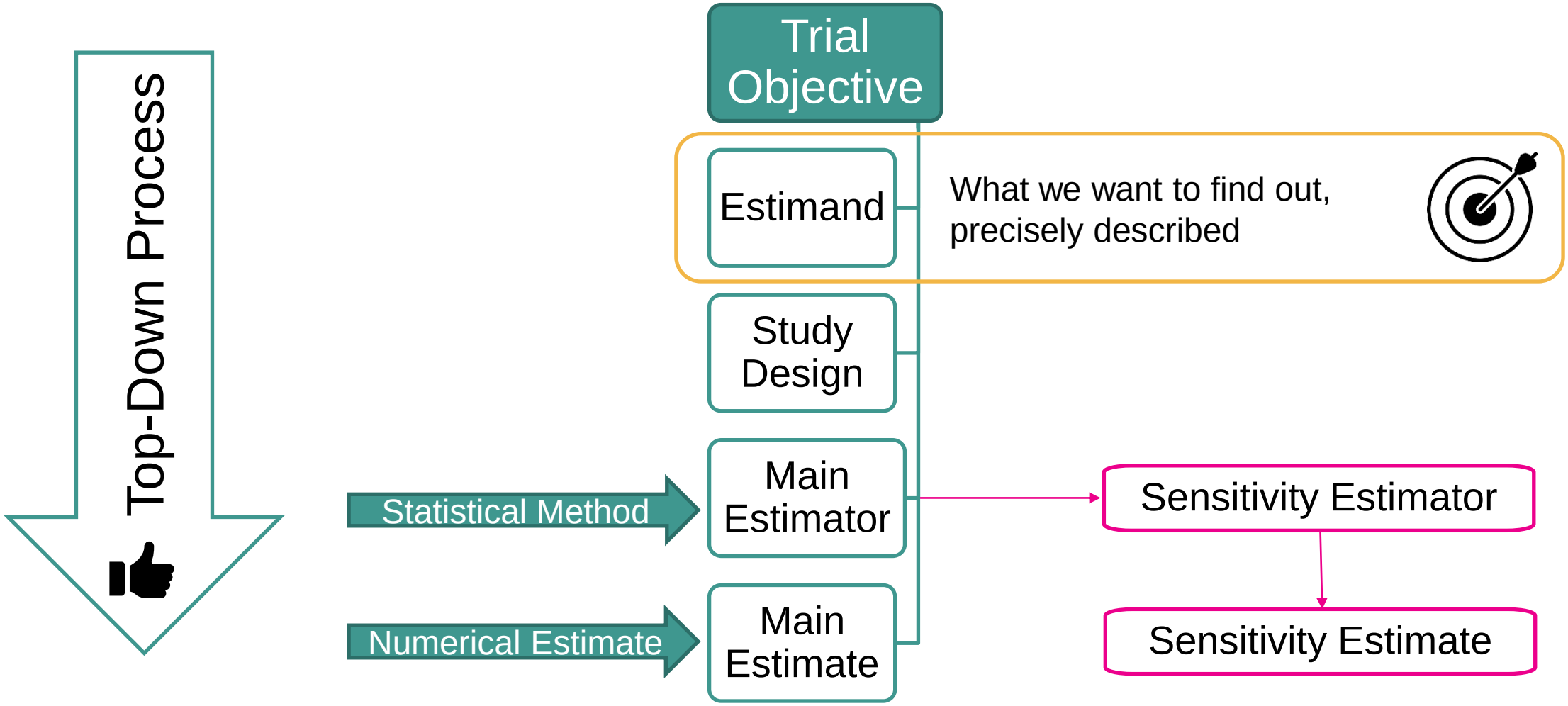
4

ICH E9 (R1) Estimand Framework

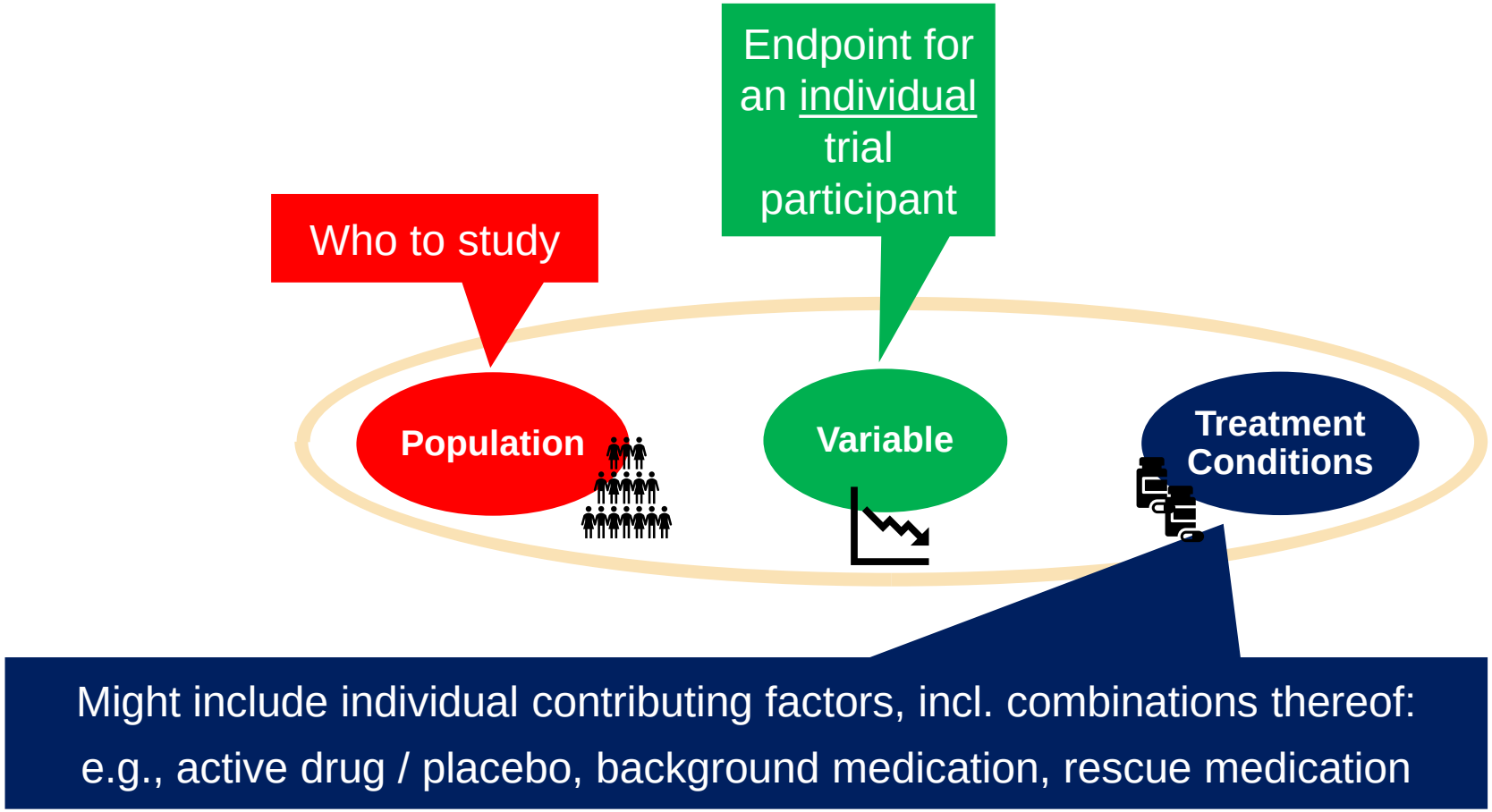
- **Promotes alignment between trial objectives, design, data collection, conduct, analysis and inference**
- Results in increased transparency and more trust in the biopharmaceutical industry
- Strengthens interdisciplinary dialogue at the design stage
  - Reduces the risk of different interpretations by relevant stakeholders (regulators, payers, patients, etc.)
- Informs what data to collect
- Aligns expectations between drug developers and regulatory bodies
- Requires a more precise definition of trial objective and meaningful treatment effect (i.e., an estimand)



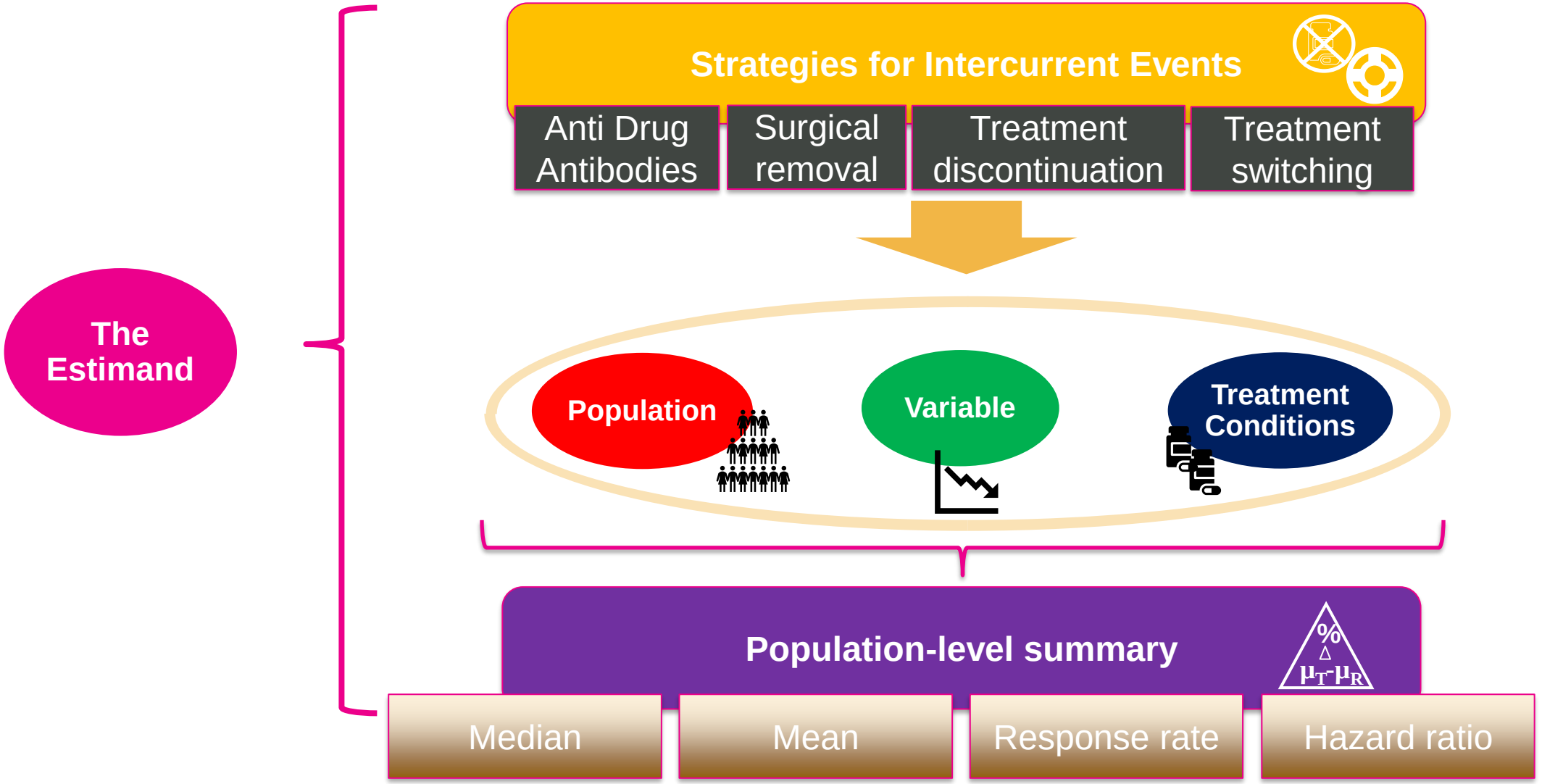
What is an estimand?



Five Components of an Estimand



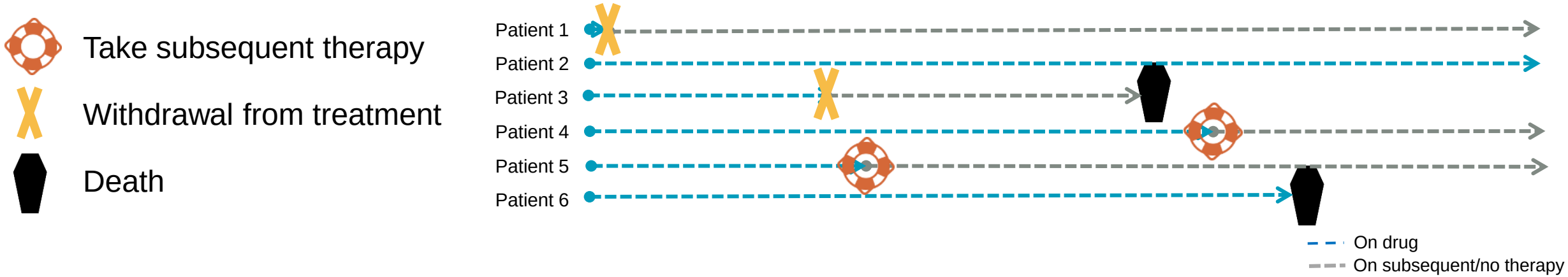
Five Components of an Estimand



Intercurrent Events

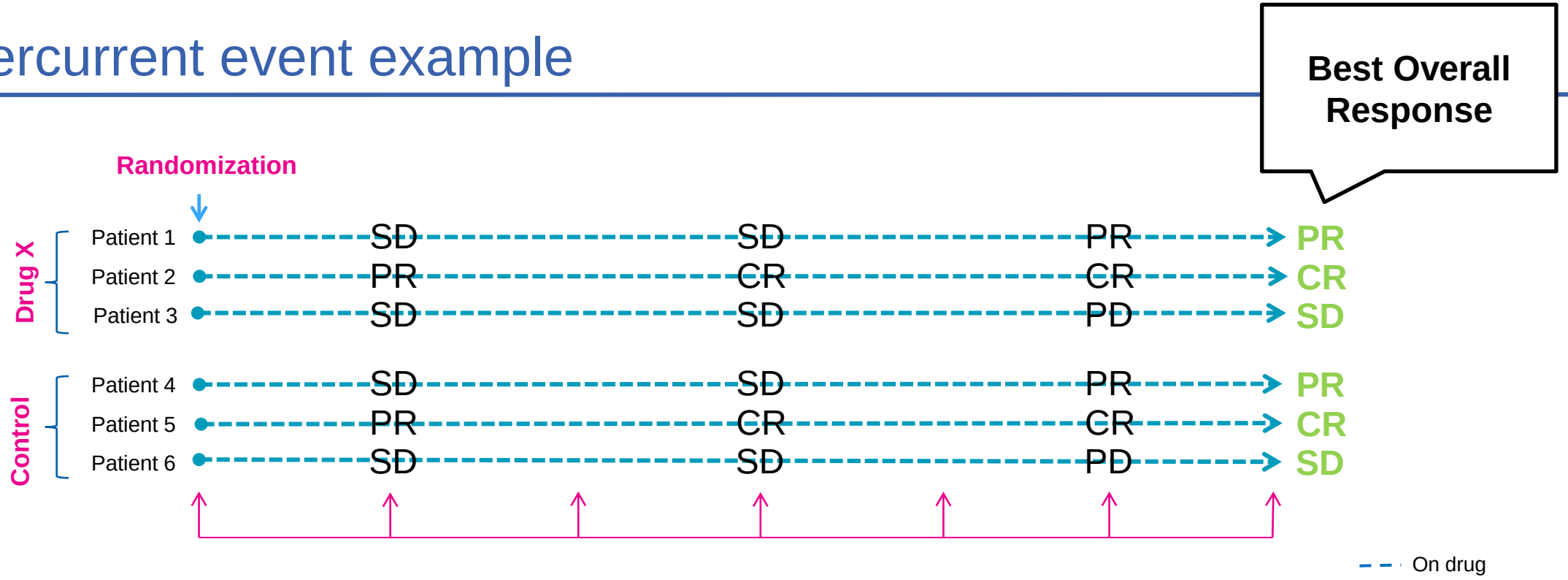
Intercurrent Events: (ICH E9 Addendum Glossary)

Events occurring after treatment initiation that either prevent the observation of the variable or affect its interpretation



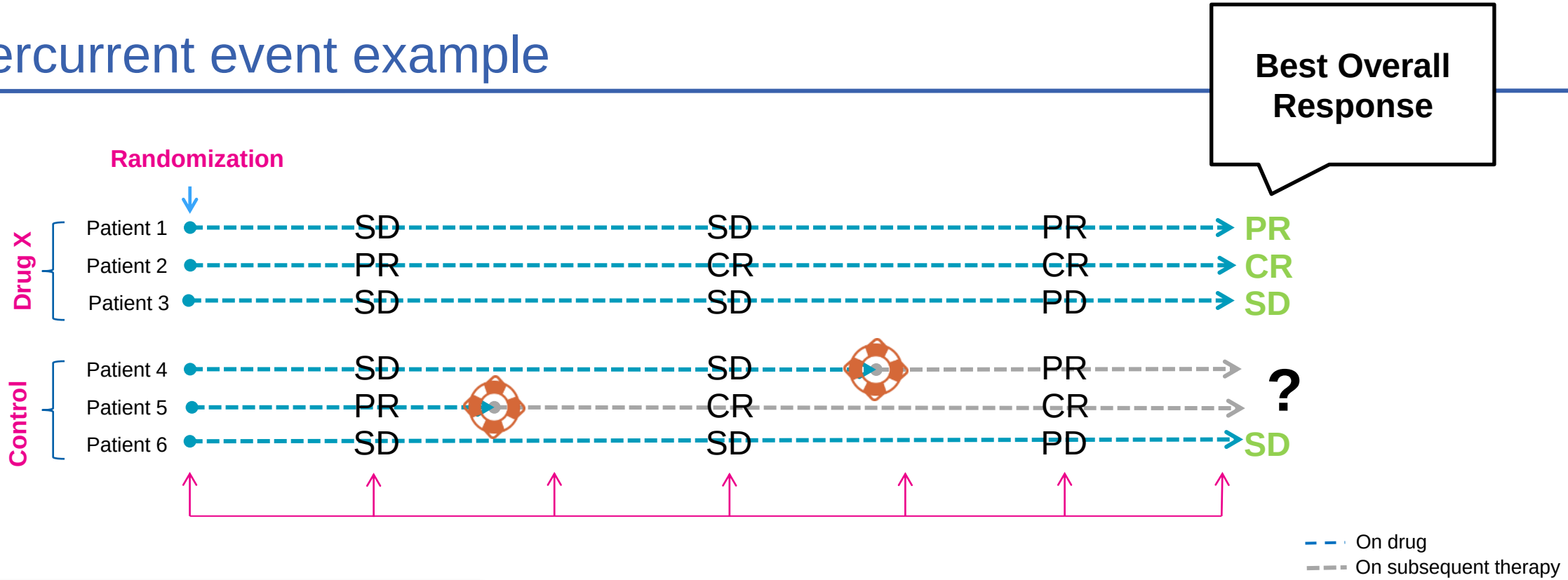
- In an estimands framework, it is necessary to:
  - Understand the actual reasons for intercurrent events
  - Understand the impact these events might have on the interpretation of the actual data in light of the research question
  - Pre-plan for them in close cooperation with study team members from different disciplines

Intercurrent event example



Best Overall Response	Primary Endpoint Objective Response
Complete Response (CR)	Objective Response
Partial Response (PR)	Objective Response
Stable Disease (SD)	Non-Responder
Progressive Disease (PD)	Non-Responder

Intercurrent event example



Take subsequent therapy

- The treatment effect might be influenced by subsequent therapy
- In this case, subsequent therapy would be an ‘Intercurrent Event’

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease

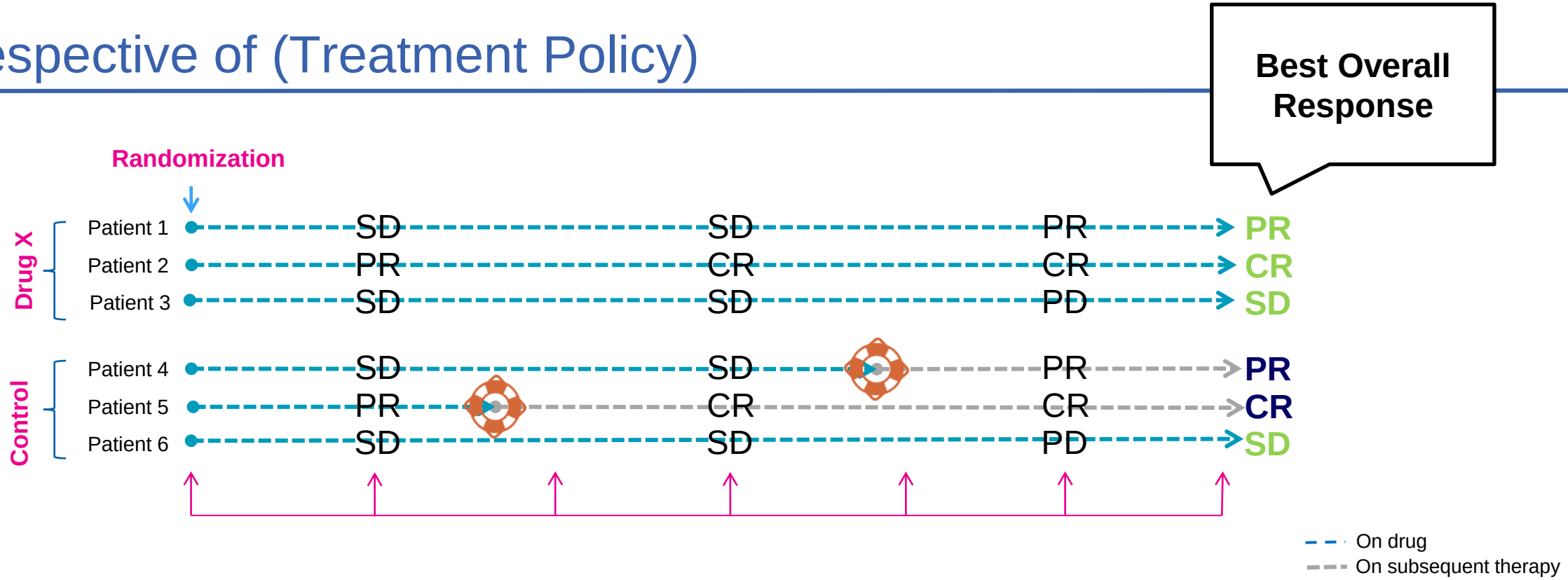
5 Strategies for Intercurrent Events

Irrespective of

- Outcome after intercurrent event is still of interest
- Data should be collected after intercurrent event

Treatment Policy

Irrespective of (Treatment Policy)



Study Treatment + Subsequent therapy

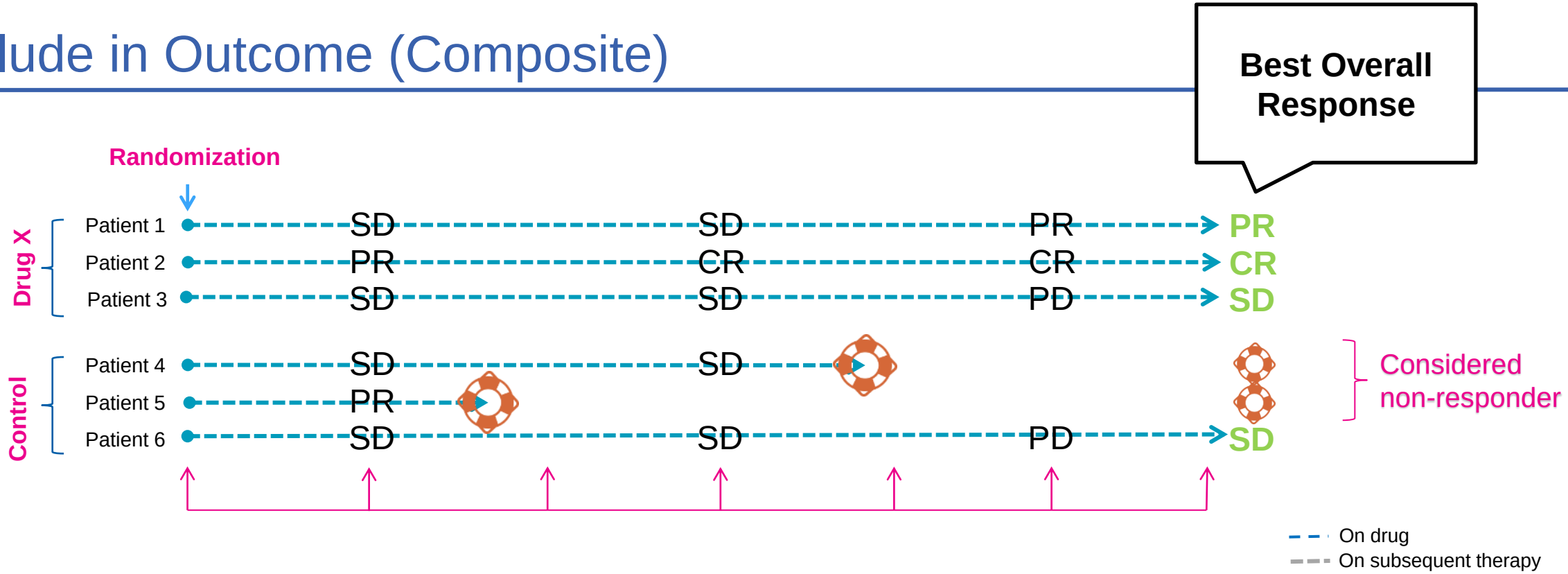
- The treatment effect for Drug X irrespective of / together with subsequent therapy (taken as required) is of interest.
- In this case, subsequent therapy would be reflected in the ‘Treatment Conditions’ attribute of the Estimand.

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease

5 Strategies for Intercurrent Events

Irrespective of	Include in Outcome
• Outcome after intercurrent event is still of interest • Data should be collected after intercurrent event	• Define composite endpoint including the intercurrent event • Intercurrent event is informative for effect of interest
Treatment Policy	**Composite**

Include in Outcome (Composite)



Variable + Subsequent therapy

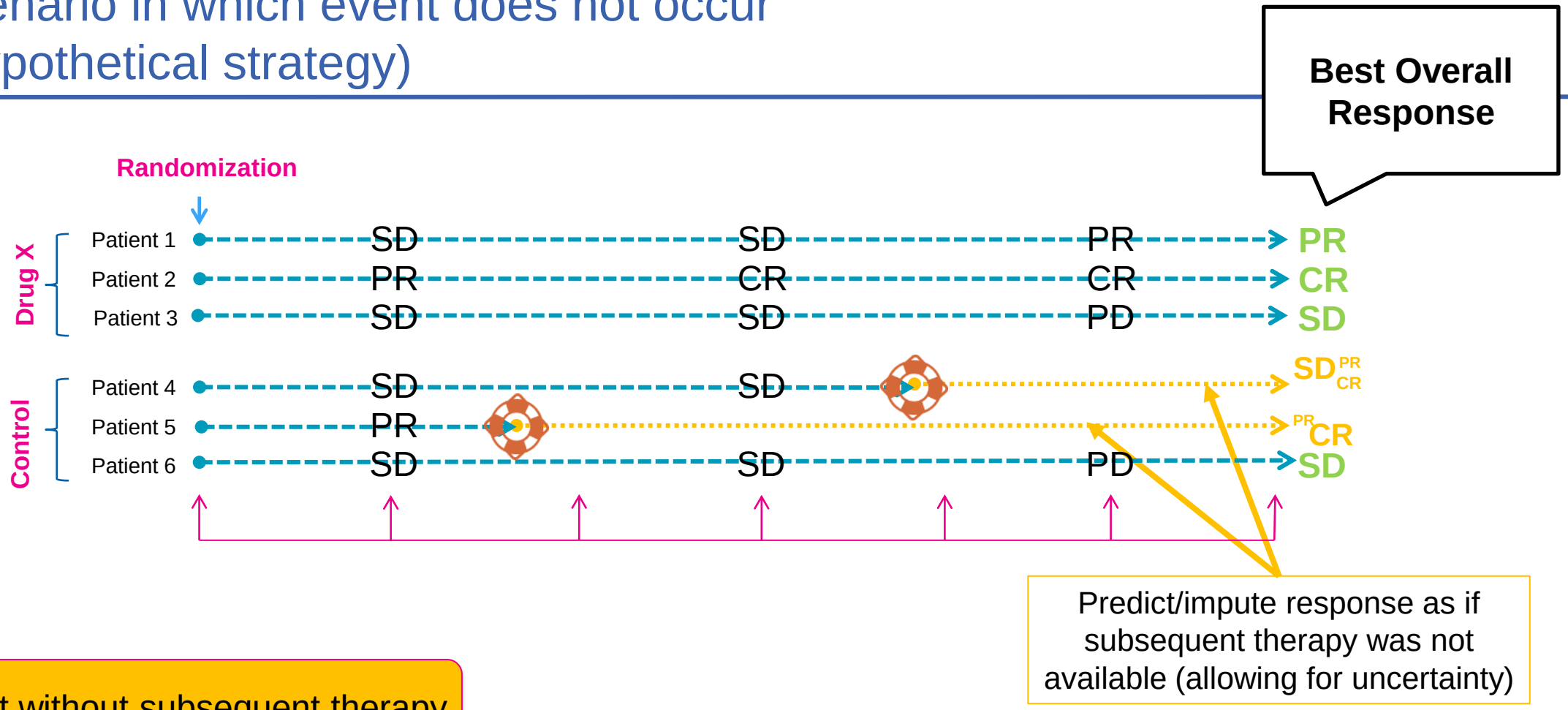
- If subsequent therapy intake is considered an **undesirable outcome,** subsequent therapy **could become part of the endpoint** of the trial.
- A patient who receives a subsequent therapy is considered a non-responder.

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease

5 Strategies for Intercurrent Events

Irrespective of	Include in Outcome	Scenario in which event does not occur
• Outcome after intercurrent event is still of interest • Data should be collected after intercurrent event	• Define composite endpoint including the intercurrent event • Intercurrent event is informative for effect of interest	• A scenario is envisaged in which the intercurrent event would not occur
Treatment Policy	**Composite**	**Hypothetical**

Scenario in which event does not occur (Hypothetical strategy)



Predict without subsequent therapy

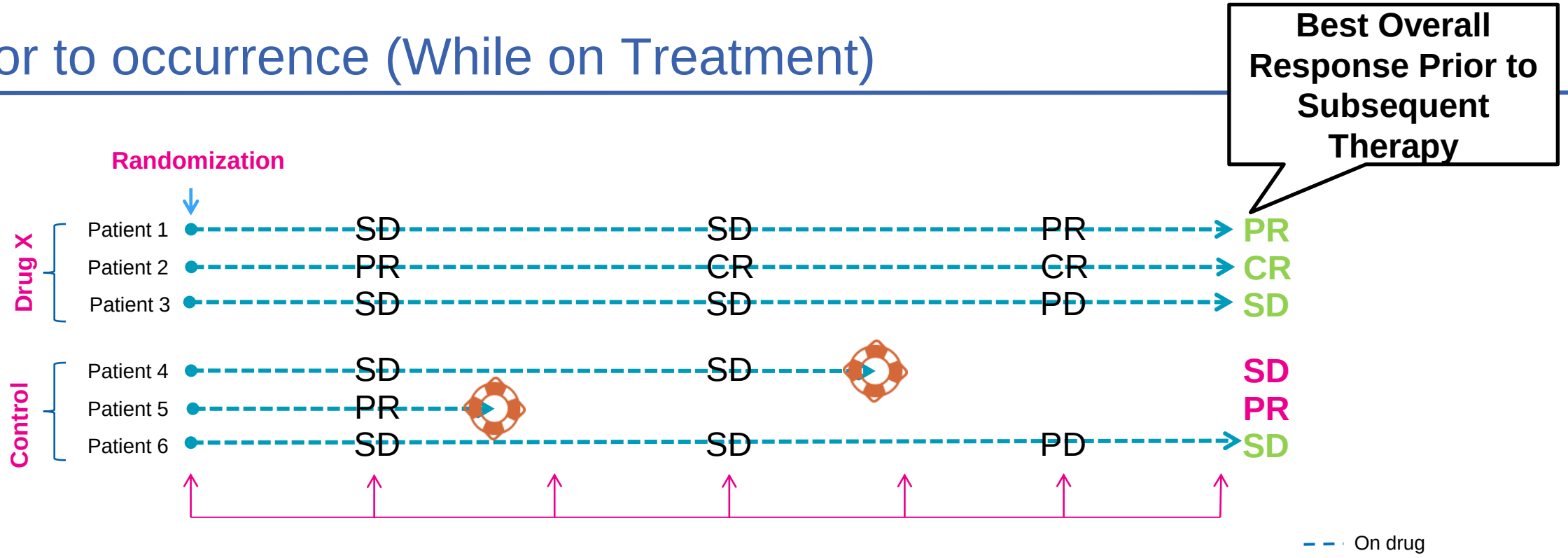
- The treatment effect for Drug X **as if subsequent therapy was not available**, is of interest.
- Hypothetical strategy for subsequent therapy would be reflected in the '**Strategies for intercurrent events**' attribute of the Estimand.

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease

5 Strategies for Intercurrent Events

Irrespective of	Include in Outcome	Scenario in which event does not occur	Prior to occurrence
• Outcome after intercurrent event is still of interest • Data should be collected after intercurrent event	• Define composite endpoint including the intercurrent event • Intercurrent event is informative for effect of interest	• A scenario is envisaged in which the intercurrent event would not occur	• Scientific question is about what happened prior to the intercurrent event • Outcome after intercurrent event is considered irrelevant
Treatment Policy	**Composite**	**Hypothetical**	**While on Treatment**

Prior to occurrence (While on Treatment)



Variable prior to subsequent therapy

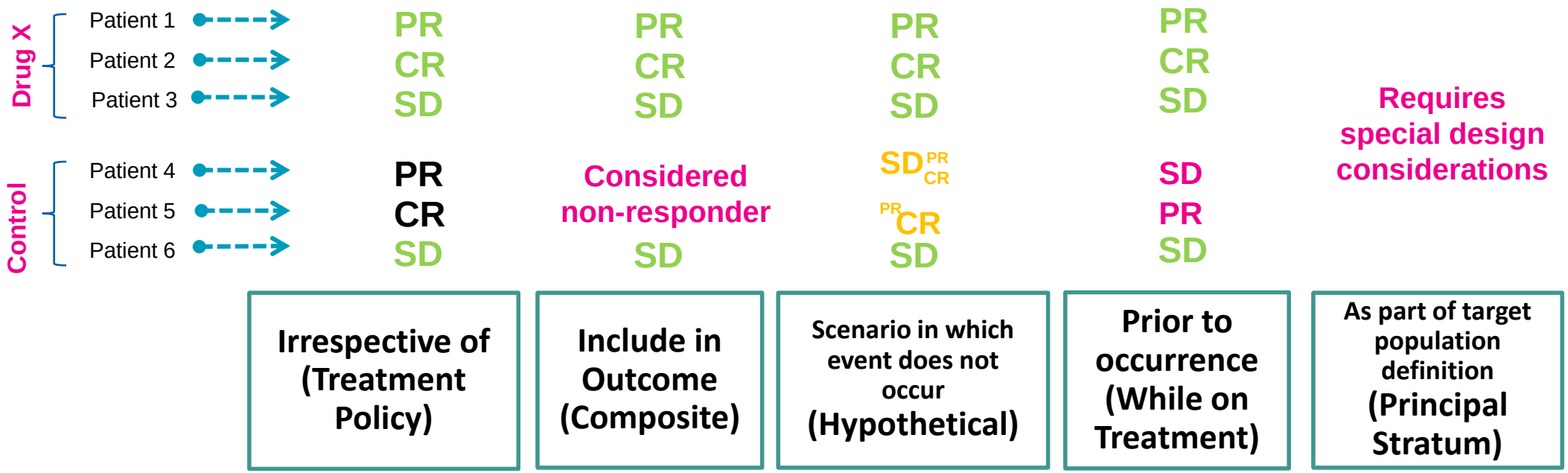
- Treatment effect prior to receiving subsequent anticancer therapy
- This strategy modifies the endpoint to “best response prior to subsequent therapy”

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease

5 Strategies for Intercurrent Events

Irrespective of	Include in Outcome	Scenario in which event does not occur	Prior to occurrence	As part of target population definition
• Outcome after intercurrent event is still of interest • Data should be collected after intercurrent event	• Define composite endpoint including the intercurrent event • Intercurrent event is informative for effect of interest	• A scenario is envisaged in which the intercurrent event would not occur	• Scientific question is about what happened prior to the intercurrent event • Outcome after intercurrent event is considered irrelevant	• Population is defined by those in whom the intercurrent event would or would not occur
Treatment Policy	**Composite**	**Hypothetical**	**While on Treatment**	**Principal Stratum**

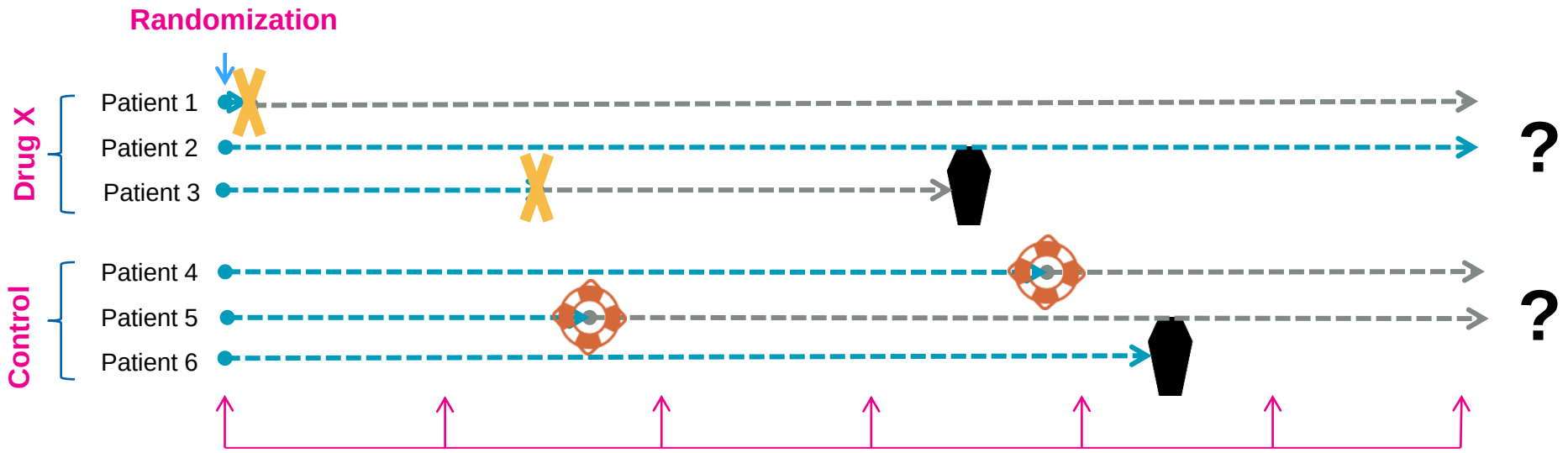
5 Strategies – 5 Answers, to different questions



- There is no universal ‘correct’ strategy
- The Estimand Framework helps to make implicit assumptions transparent and helps to align at the design stage the team/sponsor/regulators on the clinical questions of interest

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease

Real Life



Take subsequent therapy

Withdrawal from treatment

Death

Same approach

1. **Identify and plan for relevant intercurrent events**
2. **Align on suitable strategy for each of them**

Checkmate-37: Revisiting

Primary objective: “To show superiority in overall survival of nivolumab over chemotherapy” – but what exactly does that mean?

Intercurrent Event
Patient opted out of prescribed treatment
Checkpoint inhibitor therapy received

Checkmate-37: Revisiting

Primary objective: “To show superiority in overall survival of nivolumab over chemotherapy” – but what exactly does that mean?

Intercurrent Event	Primary Analysis
Patient opted out of prescribed treatment	**Irrespective of (Treatment Policy)**
Checkpoint inhibitor therapy received	**Irrespective of (Treatment Policy)**
Question of interest	Survival benefit after prescription of Nivolumab vs Chemo regardless of whether patients take assigned treatment or receive other therapy

Assumes whatever happens after randomization reflects clinical practice

Did not anticipate treatment switching to drugs with same mechanism of action

Estimand for the Primary Analysis

The target of estimation:

The treatment effect of Nivolumab compared with investigator's choice chemotherapy for patients with advanced melanoma who progressed on or after ipilimumab measured by the hazard ratio of overall survival, regardless of whether the subject opted out of prescribed treatment or receive other therapy.

Strategies for Intercurrent Events

Population

Variable

Treatment Conditions

Population-level summary

Checkmate-37: Revisiting

Primary objective: “To show superiority in overall survival of nivolumab over chemotherapy” – but what exactly does that mean?

Intercurrent Event	Primary Analysis	Post-Hoc Analysis
 Patient opted out of prescribed treatment	**Irrespective of (Treatment Policy)**	**Subgroup analysis (?)**
 Checkpoint inhibitor therapy received	**Irrespective of (Treatment Policy)**	**Predict (Hypothetical)**
Question of interest	Survival benefit after **prescription** of Nivolumab vs chemotherapy regardless of whether patients take assigned treatment **or receive other therapy**	Survival benefit after **treatment** with Nivolumab vs chemotherapy **as if** patients **never received follow-up checkpoint inhibitor** therapy

Different questions with different answers

Estimand for the Post-Hoc Analysis

The target of estimation:

The treatment effect of Nivolumab compared with investigator's choice chemotherapy for treated patients with advanced melanoma who progressed on or after ipilimumab measured by the hazard ratio of overall survival as though subsequent immune checkpoint inhibitor treatment is not available.

Strategies for Intercurrent Events

Population

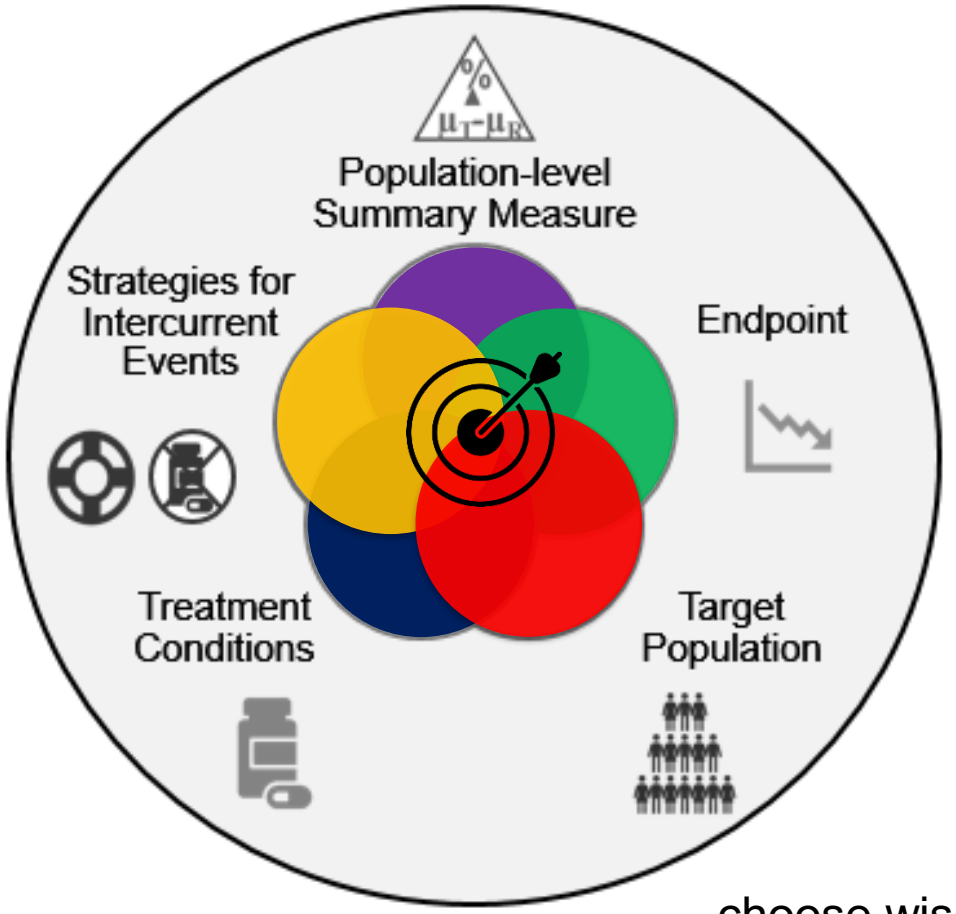
Variable

Treatment Conditions

Population-level summary

Always build your Estimand

The Estimand



… choose wisely and include it in the protocol!

Interactive Quiz!

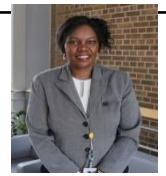
Poll 1

- What primary role is responsible for defining the estimand?
  - Statistician
  - Clinician
  - Regulatory
  - The study team
- Estimands should be discussed and developed
  - During protocol development
  - After the protocol has been finalized but prior to finalizing the statistical analysis plan
  - After finalizing the statistical analysis plan but prior to unblinding

Poll 2

- Common intercurrent events for oncology clinical trials include (check all that apply)
  - Death due to COVID
  - Start of new anticancer therapy
  - Premature discontinuation from treatment
  - Withdrawal from study
  - Concomitant radiation

Panelists

	**Lei Nie** PhD, is an associate division director from the office of Biostatistics, Office of Translational Science, at the FDA Center for Drug Evaluation and Research. Passionate about the important work performed at the FDA, he is interested in developing and promoting innovative statistical methods in drug development through communication and collaboration.	
	**Donna Przepiorka** MD, PhD, is a Clinical Team Lead in the Division of Hematological Malignancies 1 in the Office of Oncological Disease at the FDA Center for Drug Evaluation and Research	
	**Catherine Njue** Dr. Catherine Njue is the manager for the Office of Biostatistics in the Biologic and Radiopharmaceutical Drugs Directorate (BRDD), Health Canada and she leads the biostatistics team that is primarily involved in evaluating the statistical methodology of clinical trials for biologics (e.g., vaccines, blood products) and related biotechnology products and radiopharmaceuticals.	
	**Frank Bretz** Dr. Frank Bretz is a Distinguished Quantitative Research Scientist at Novartis. He has supported the methodological development in various areas of drug development, including dose finding, estimands, multiple testing, and adaptive designs. He was a member of the ICH E9(R1) Expert Working Group on 'Estimands and sensitivity analysis in clinical trials' and currently serves on the ICH E20 Expert Working Group on 'Adaptive clinical trials'.	

Panel Discussion

Please type any questions you have into the Q&A.

Slides will soon be available on: www.oncoestimand.org

Estimands in all COVID-19 Vaccine Trials

moderna

A Study to Evaluate Efficacy, Safety, and Immunogenicity of mRNA-1273 Vaccine in Adults Aged 18 Years and Older to Prevent COVID-19

Table 19: Primary Objective and Estimands with Rationale for Strategies to Address Intercurrent Events for Per-Protocol Analysis

Objective: To demonstrate the efficacy of mRNA-1273 to prevent COVID-19	
Estimand Description	Vaccine efficacy will be measured using 1 – HR (mRNA-1273/Placebo) of COVID-19 from 14 days after second dose of IP in adults. A treatment policy strategy will be used for early discontinuation (eg, withdrawal consent, deaths unrelated to COVID-19) or early infection. A principal stratum strategy is used to exclude participants missing a dose of IP or being seropositive at baseline.
Target Population	Adults aged 18 years and older in circumstances at a high risk of SARS-CoV-2 infection but without medical conditions that pose additional risk of developing severe disease. The population excludes those previously infected or vaccinated for SARS-CoV-2 or with a medical condition, on treatment that poses additional risks (including those requiring immunosuppressants or immune-modifying drugs), or pre-seropositive.
Variable/Endpoint	Time to infection, censoring at early discontinuation, early infection, or last assessment for an event not being observed, whichever comes earlier.
Treatment Condition(s)	**Test:** mRNA-1273 **Reference:** Placebo
Estimand Label	**Estimand 1**
Population-Level Summary	Vaccine efficacy defined as 1 - HR of mRNA-1273/Placebo
Intercurrent Event Strategy	
IcEv1 (Early discontinuation):	Treatment policy
IcEv2 (early infection):	Treatment policy
IcEv3 (Missed dose of IP):	Principal stratum

Source: https://clinicaltrials.gov/

AstraZeneca

Phase III Double-blind, Placebo-controlled Study of AZD1222 for the Prevention of COVID-19 in Adults

Objective [a]		Estimand [b] Description/Endpoint
PRIMARY		
1	To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19 in adults ≥ 18 years of age	**Population:** Full analysis set, excluding participants who are seropositive at baseline.
		Endpoint: A binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs ≥ 15 days post second dose of study intervention. Otherwise, a participant is not defined as a COVID-19 case.
		Intercurrent events: For participants who withdraw from the study prior to having met the criteria for the primary efficacy endpoint, absence of data following these participants' withdrawal will be treated as missing (ie, counted as not having met the criteria); participants who withdraw before 15 days post second dose or who have a case prior to 15 days post second dose will be excluded from primary endpoint analysis.
		Summary measure: VE, calculated as 1-relative risk. (Relative risk is the incidence of infection in the vaccine group relative to the incidence of infection in the control group.)

Pfizer

Study to Describe the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

3.2. For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the last dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the last dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

Your Role: Construction of Estimands

It is a multi-disciplinary undertaking and should be the subject of discussion between sponsors and regulators