The Estimands Academy for Trial Teams

"Bringing estimands to *life* through real case studies"

Webinar 2: Estimands in Oncology - How and Why

US/EU webinar: 1st of June 2021 3-4:30 pm UK /4-5:30 pm CET/10-11:30 am EST/7-8:30 am Pacific time

EU/ASIA webinar: 2nd of June 2021 9-10:30 am UK/10-11:30 am CET/4-5:30 pm Shanghai

EFSPI

European Federation of Statisticians in the Pharmaceutical Industry
Representing Statistical Associations in Europe

efpia
European Federation of Pharmaceutical
Industries and Associations

PSI

EFPIA / EFSPI Estimand Implementation Working Group (EIWG)

EIWG brings together statisticians and clinicians to support the estimand journey

Estimand Implementation Working Group (EIWG) Members

Institution	Member
AMGEN	Mary Elliott-Davey
AstraZeneca	David Wright
BAYER	Vivian Lanius
Boehringer Ingelheim	James Bell
CONSILIUM Salmonson & Hemmings	Rob Hemmings*
PT Stat Consulting	Paul Terrill
gsk	**Chrissie Fletcher+**
gsk	Oliver Keene
gsk	Jatin Patel (C)
gsk	Millie Wang (C)

Institution	Member
IQVIA	Maria Efstathiou
LEO	Christian Pipper
Lilly	Pepa Polavieja
Lundbeck	**Nanco Hefting+ (C)**
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MERCK	Armin Schueler
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novo nordisk	Rikke Mette Agesen (C)
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Institution	Member
MHRA	Khadija Rantell
Pfizer	Maria Dilleen
Pfizer	Rod Junor (C)
PPD	Sue McKendrick
PPD	Nikolay Stoyanov (C)
Roche / SERVIER	Judith Anzures-Cabrera
Roche / SERVIER	Estelle Lambert
ucb	Christian Loesch
ucb	Katsumi Yoshida
ucb	Amel Besseghir

+Co-Lead   *Adhoc member   C = Clinician

Disclaimer

◆ Opinions are those of the presenters and are not necessarily the views of the respective companies.

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

Introductions

	Kaspar Rufibach is an Expert Statistical Scientist in Roche's Methods, Collaboration, and Outreach group and located in Basel. He has **co-founded and co-leads** the European special interest group "**Estimands in oncology**". **Moderator of June 2 session**	Roche
	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 June 1 session and Co-Presenter June 2**	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 June 1**	Pfizer
	Feng Liu has 20+ years of experience in pharmaceutical drug development working for Intercept Pharma. **Co-Presenter June 1**	Intracept
	Rui (Sammi) Tang is the Head of Biostatistics, Programming and Medical Writing Department at Servier Pharmaceuticals US. **Co-Presenter June 1**	SERVIER
	Jiawei Wei is currently a Director Statistical Consultant in the Advanced Methodology and Data Science group at Novartis. **Co-Presenter June 2**	NOVARTIS
	Giovanna Andreola, MD, is a board-certified oncologist with several years of clinical experience in hematology and stem cell transplantation working at Novartis. **Co-Presenter June 2**	
	Jonathan Siegel is Director of Oncology Clinical Statistics US at Bayer with over 20 years' experience in pharmaceutical oncology in multiple companies.	BAYER

Acknowledgements

Our sincere thanks to:

◆ To EFPIA/EFSPI for sponsoring and promoting the webinar.

◆ To EIWG members for the lively discussion and comments on the slides.

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 on estimands in oncology

Agenda

Introductions, Acknowledgements and Learning Outcomes

Introduction to the case study

Intermezzo

Estimands in Oncology – How and Why

Revisiting the case study

Interactive Quiz with Q&A

Concluding Remarks

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.

Patients with advanced melanoma who progressed on or after ipilimumab (and BRAF, if BRAF V600+)	Open Label 2:1 Randomization →	Test: Nivolumab (Nivo)
	→	Reference: Investigator's choice chemotherapy (ICC)

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)

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)

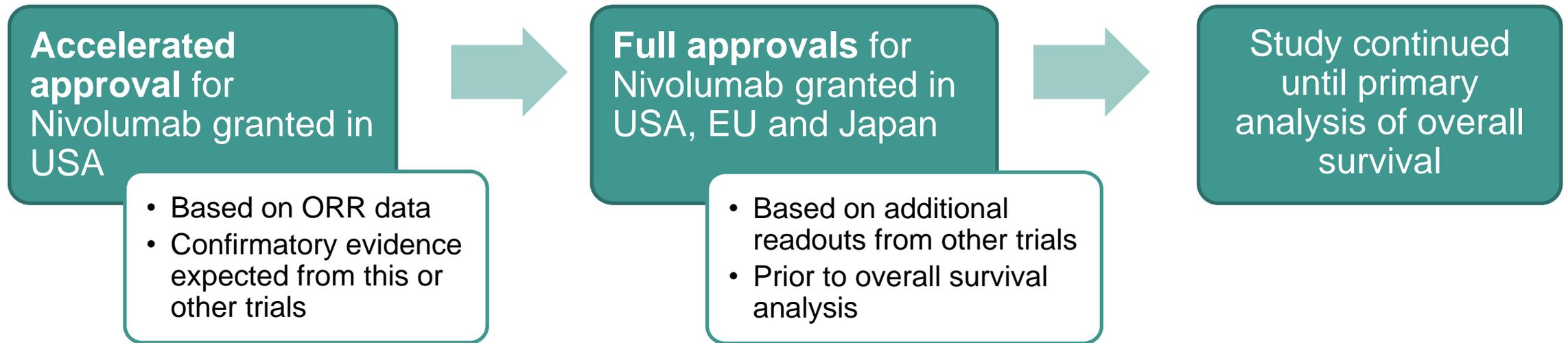Defined as the proportion of subjects who had achieved an objective response. Used as an early indicator of activity.

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

→

Full approvals for Nivolumab granted in USA, EU and Japan

→

Study continued until primary analysis of overall survival

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

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

Checkmate-37: Final assessment of Overall Survival

Overall survival: Hazard Ratio = 0.95, median overall survival 15.7 months vs 14.4 months
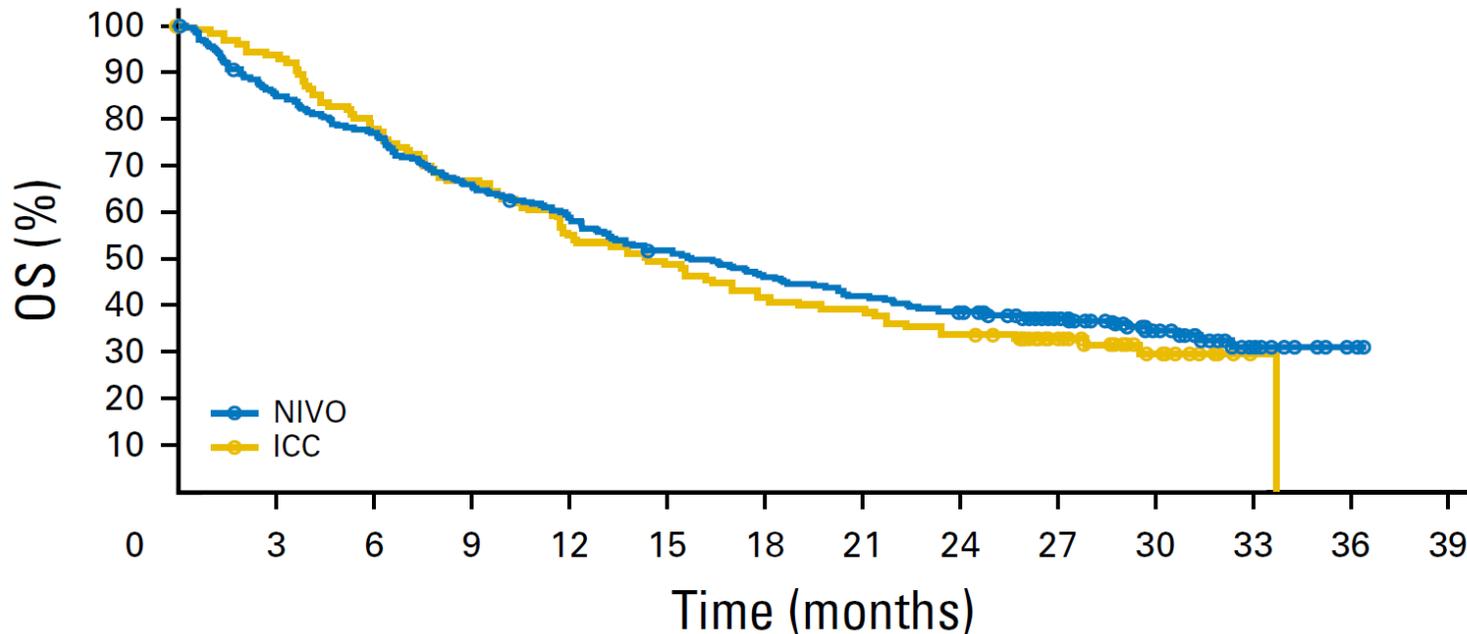
CheckMate 037: Nivolumab Improved Responses, Not Survival in Advanced Melanoma

July 17, 2017
Leah Lawrence

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

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

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

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-

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ELSEVIER   Journal of Clinical Epidemiology
            Volume 127, November 2020, Pages 1-8   JCE

Original Article

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

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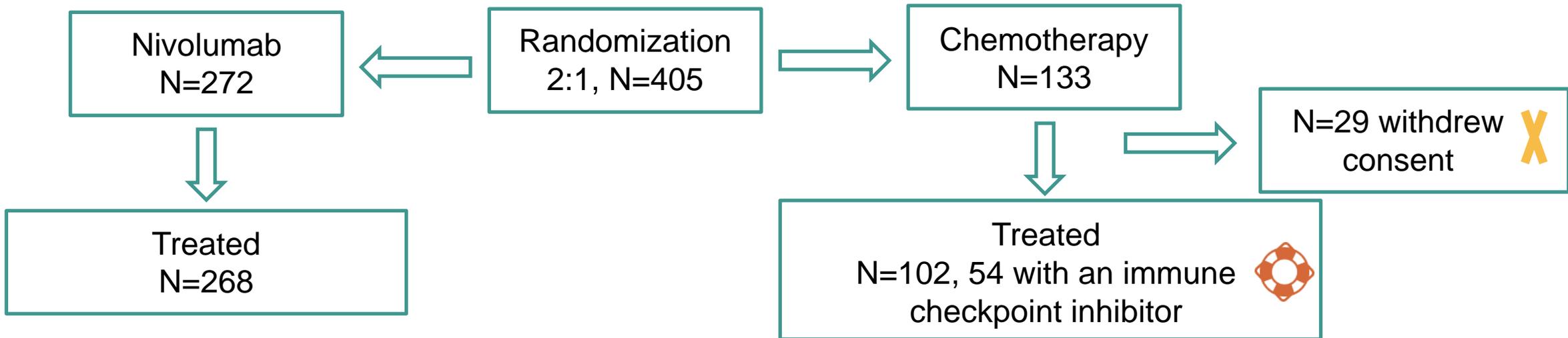
Observation	
Patient opted out of prescribed treatment	Pre-treatment: 22% in chemotherapy-arm withdrew consent immediately after randomization
Checkpoint inhibitor therapy received (drug from same class)	Post-treatment discontinuation: at least 41% in chemotherapy-arm received another checkpoint inhibitor

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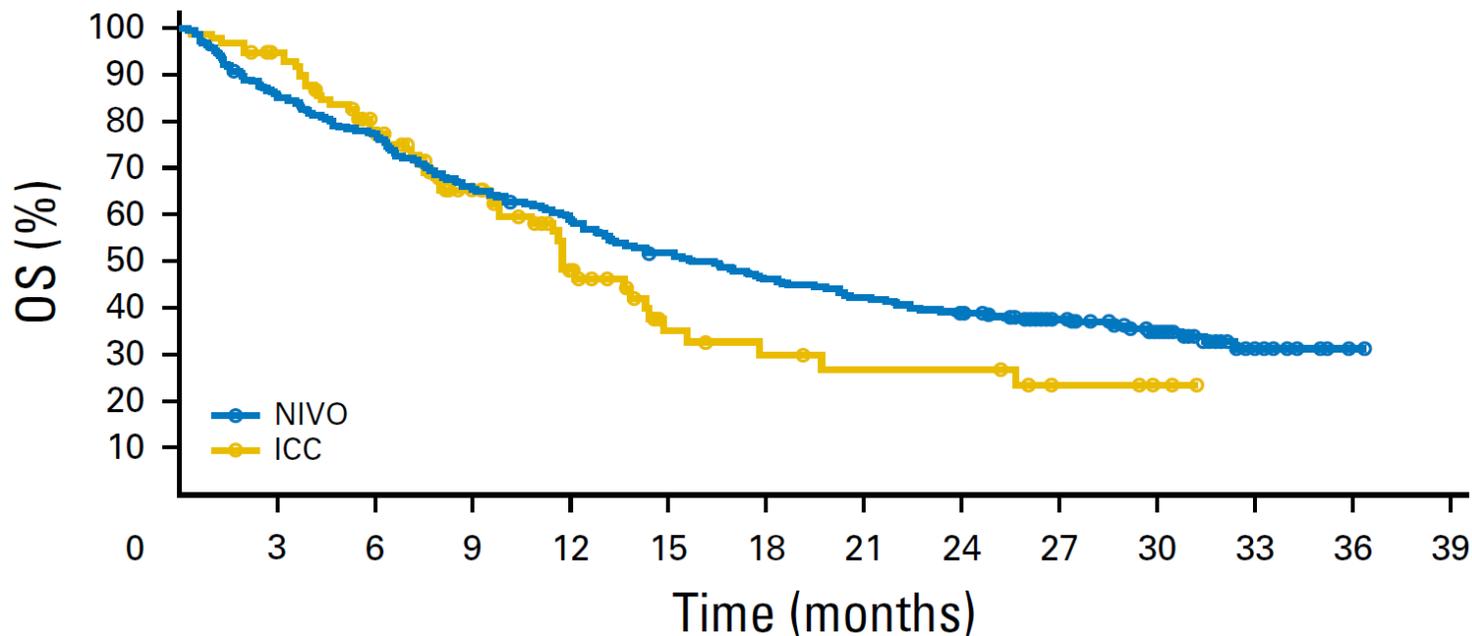
CheckMate 037: Nivolumab Improved Responses, Not Survival in Advanced Melanoma

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

Built upon: xcpd (CC BY-NC 2.5)
https://xkcd.com/1192/

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)

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

What is an estimand?

Top-Down Process

Trial Objective

Estimand — What we want to find out, precisely described

Study Design

Statistical Method → Main Estimator → Sensitivity Estimator

Numerical Estimate → Main Estimate → Sensitivity Estimate
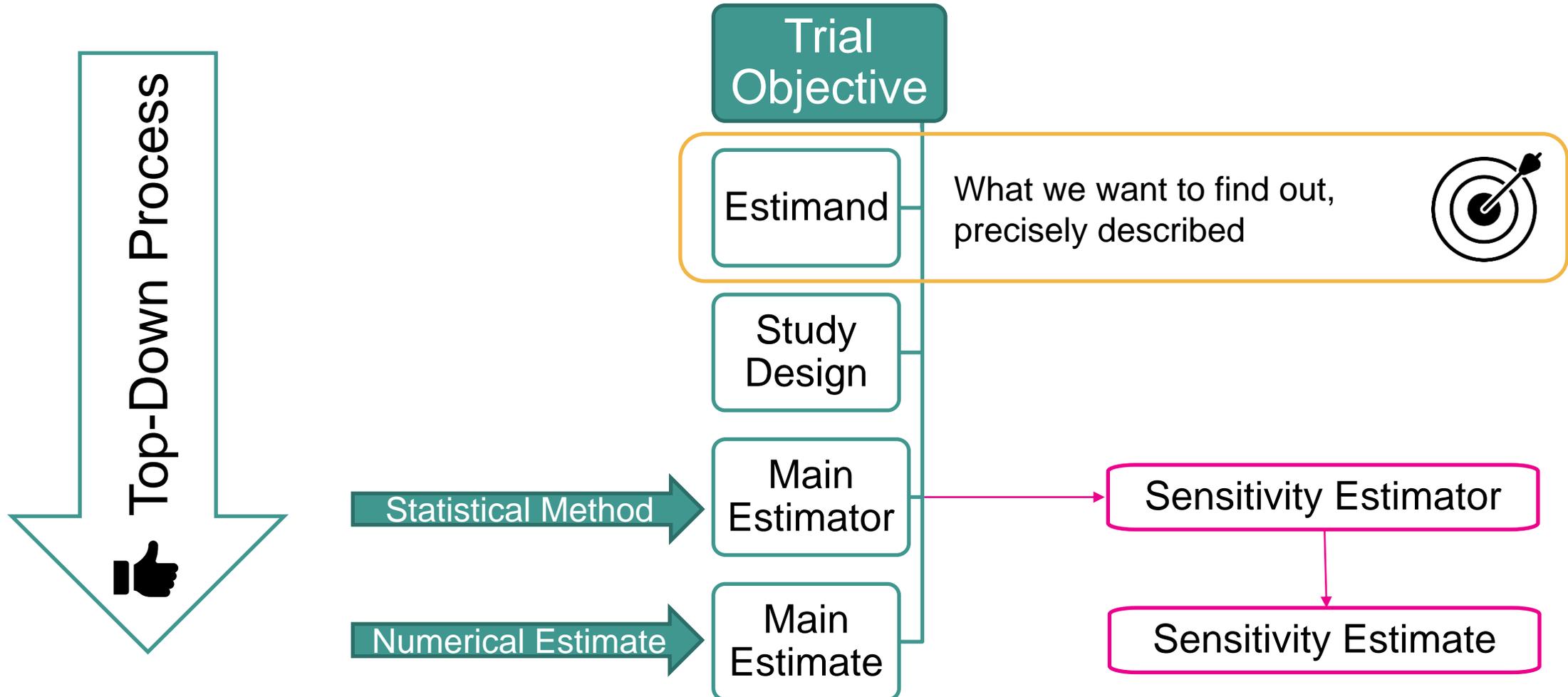
Remind yourself of the Soup analogy in the first webinar
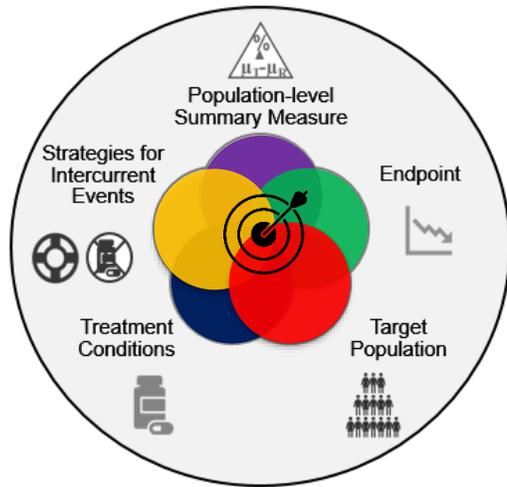
The Estimand WHAT type of soup?

Recipe
Ingredients

The Estimator
(statistical methods)

HOW to cook
the soup

The Estimate of the
treatment effect
(numerical result)

RESULT!
The tasty soup!

Five Components of an Estimand

Who to study

Endpoint for an <u>individual</u> trial participant

Population

Variable

Treatment Conditions
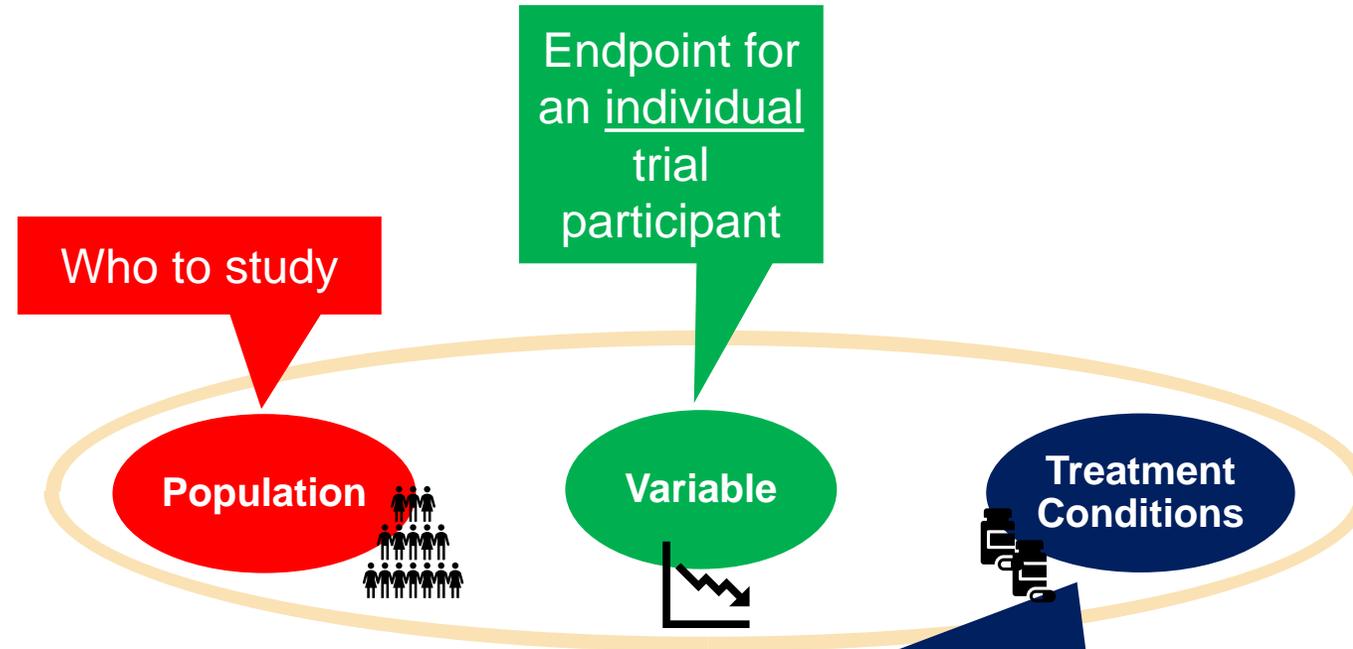
Might include individual contributing factors, incl. combinations thereof:
e.g., active drug / placebo, background medication, rescue medication

Five Components of an Estimand

The Estimand

Strategies for Intercurrent Events

| Anti Drug Antibodies | Surgical removal | Treatment discontinuation | Treatment switching |

Population

Variable

Treatment Conditions

Population-level summary

$$\mu_T - \mu_R$$

| Median | Mean | Response rate | Hazard ratio |
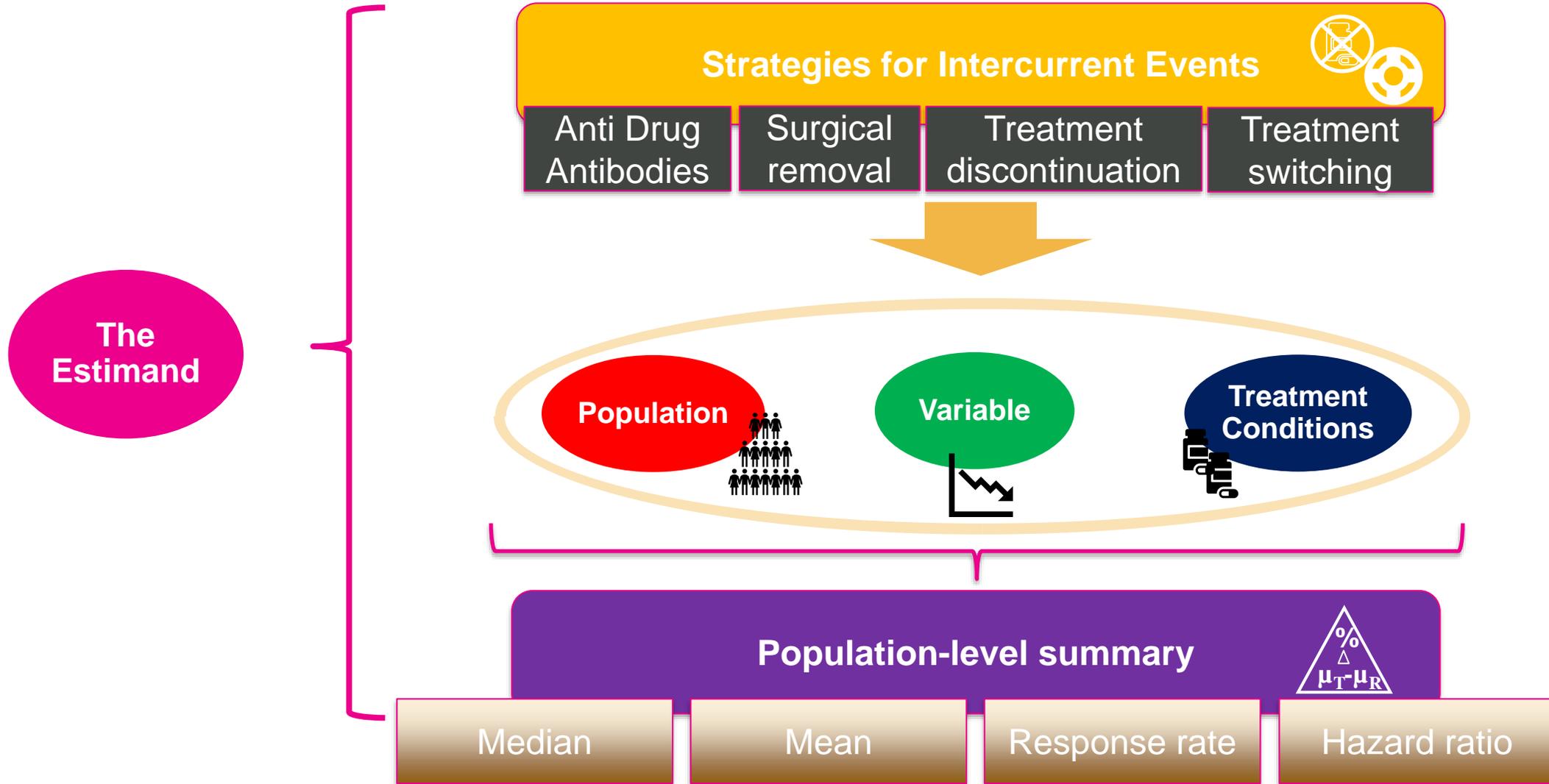
Strategies for Intercurrent Events

> **Intercurrent Events: (ICH E9 Addendum Glossary)**
>
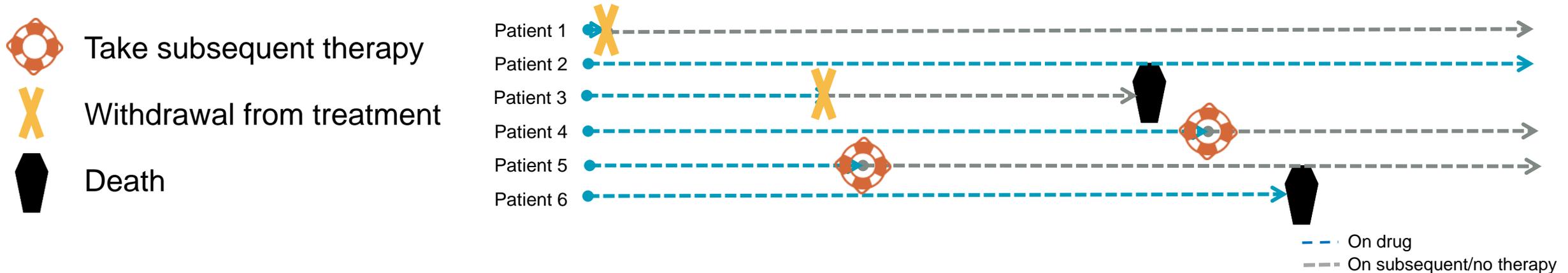> Events occurring after treatment initiation that either prevent the observation of the variable or affect its interpretation

- **Take subsequent therapy**
- **Withdrawal from treatment**
- **Death**

Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6

– – – On drug
– – – On subsequent/no therapy

◆ 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

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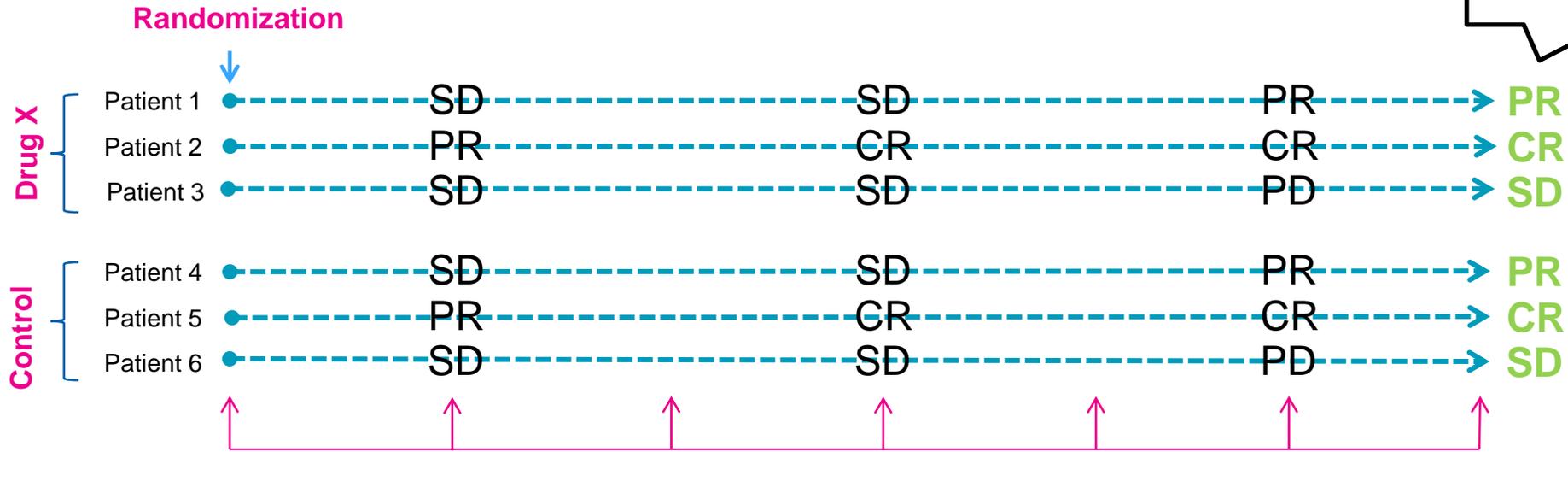
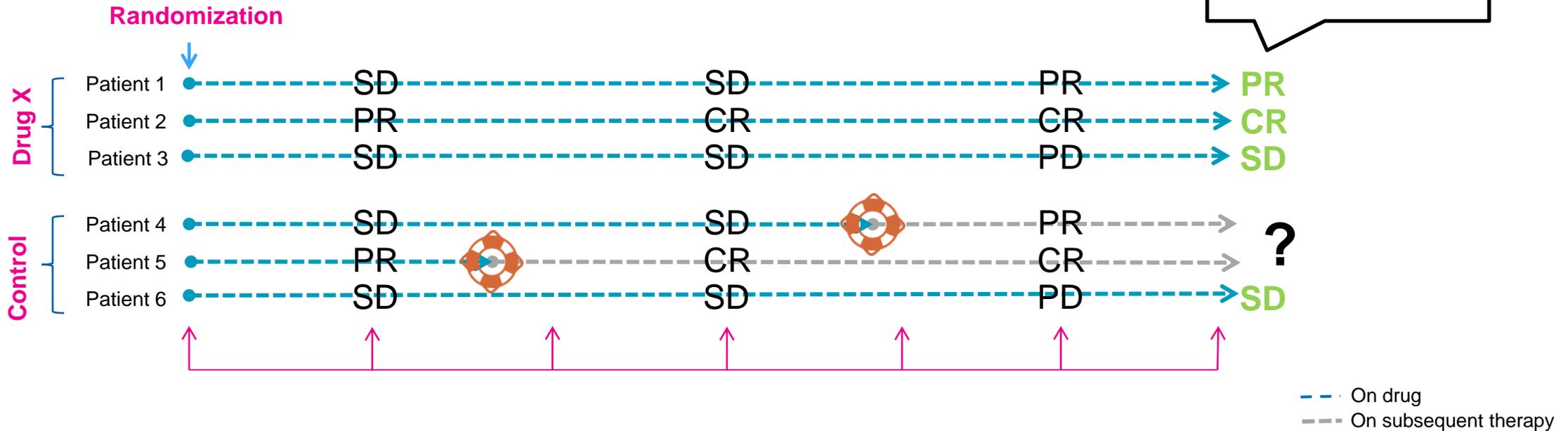| Best Overall Response	Primary Endpoint Objective Response
Complete Response (CR)	Objective Response
Partial Response (PR)	Objective Response
Stable Disease (SD)	Non-Responder
Progressive Disease (PD)	Non-Responder

Patient Profiles

Best Overall Response

Randomization

		SD	SD	PR	**PR**
Drug X	Patient 1	SD	SD	PR	**PR**
	Patient 2	PR	CR	CR	**CR**
	Patient 3	SD	SD	PD	**SD**

Control	Patient 4	SD	SD		PR	**?**
	Patient 5	PR		CR	CR	
	Patient 6	SD	SD	PD	**SD**

– – – On drug
- - - On subsequent therapy

Take subsequent therapy

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

25

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease
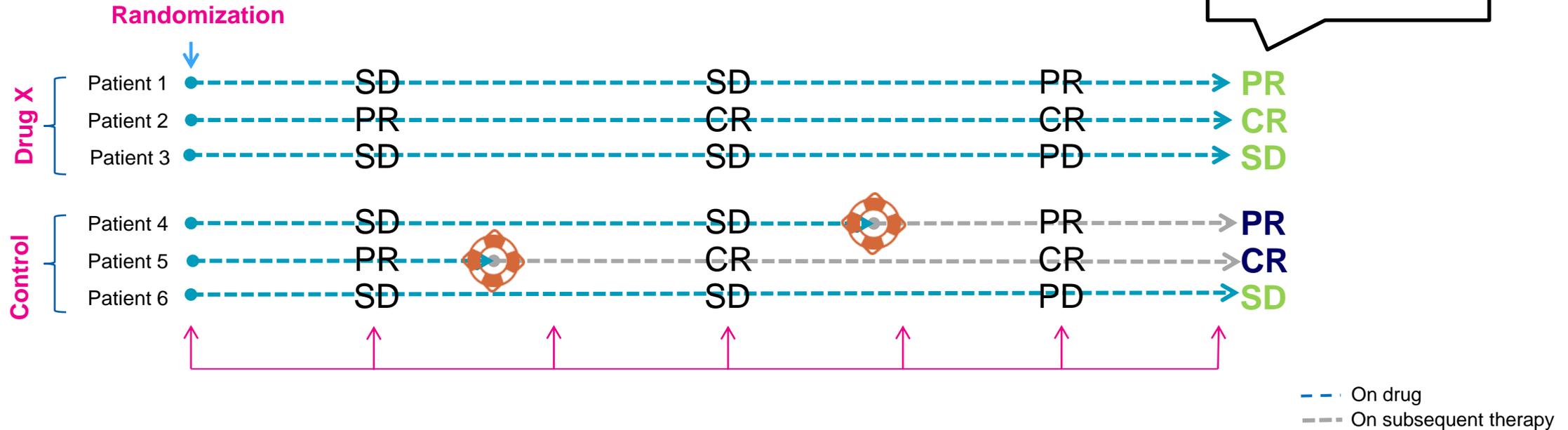
5 Strategies for Intercurrent Events

Irrespective of

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

Treatment Policy

Irrespective of (Treatment Policy)

Best Overall Response

Randomization

		SD	SD	PR	**PR**
Drug X	Patient 1	SD	SD	PR	PR
	Patient 2	PR	CR	CR	CR
	Patient 3	SD	SD	PD	SD
Control	Patient 4	SD	SD	PR	PR
	Patient 5	PR	CR	CR	CR
	Patient 6	SD	SD	PD	SD

- - On drug
- - - On subsequent therapy

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

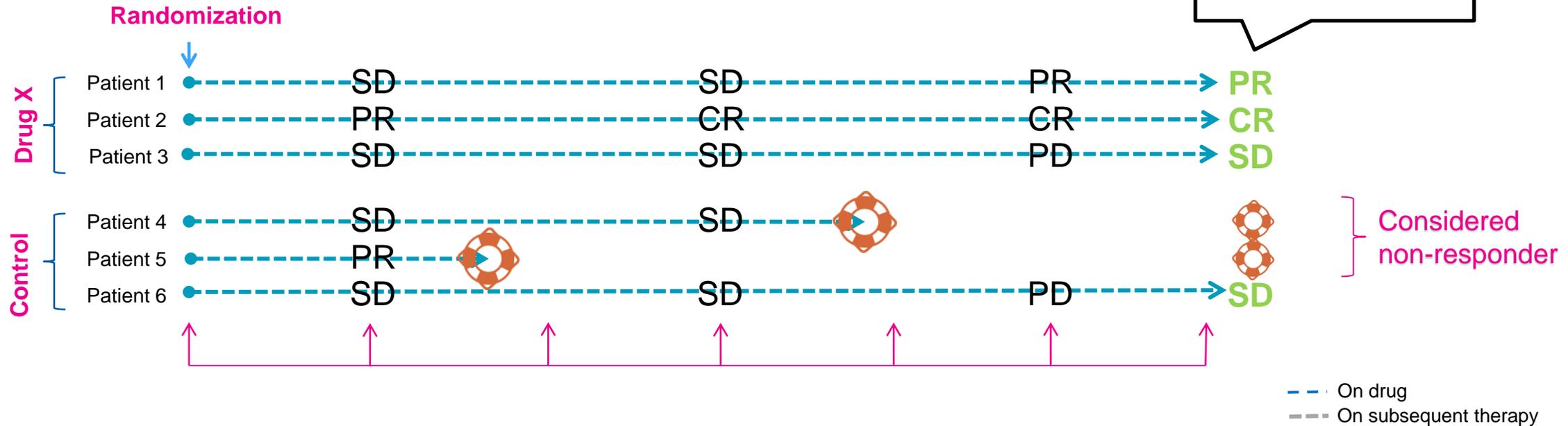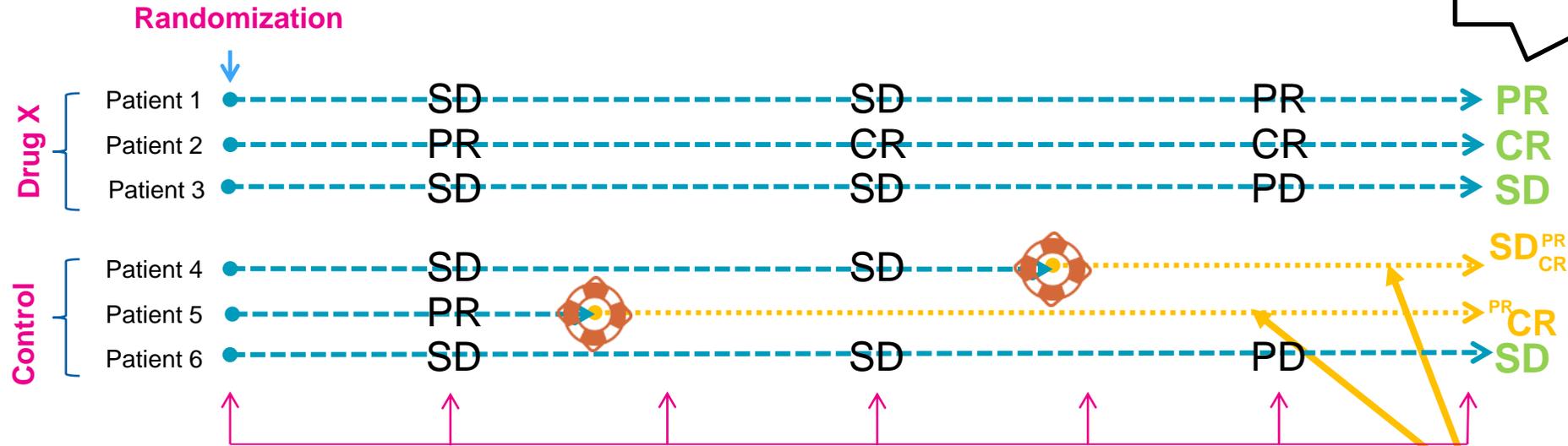| Irrespective of	Include in Outcome
• Outcome after intercurrent event is still of interest • Data should be collected after intercurrent event	• Define composite endpoint including the intercurrent event • Intercurrent event is informative for effect of interest
Treatment Policy	**Composite**

Include in Outcome (Composite)

- 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)

Best Overall Response

Randomization

Drug X	Patient 1	SD	SD	PR → **PR**
	Patient 2	PR	CR	CR → **CR**
	Patient 3	SD	SD	PD → **SD**
Control	Patient 4	SD	SD	→ SD^{PR}_{CR}
	Patient 5	PR		→ ^{PR}CR
	Patient 6	SD	SD	PD → **SD**

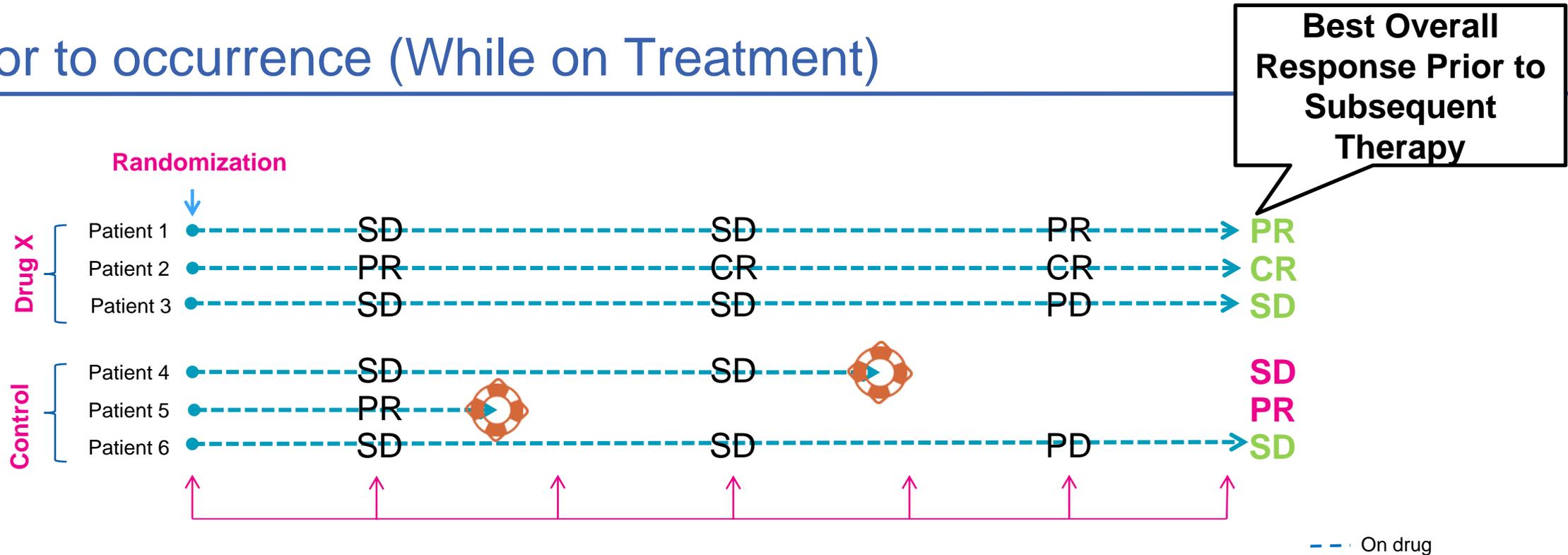**Predict without subsequent therapy**

Predict/impute response as if subsequent therapy was not available (allowing for uncertainty)

- 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)

Best Overall Response Prior to Subsequent Therapy

Randomization

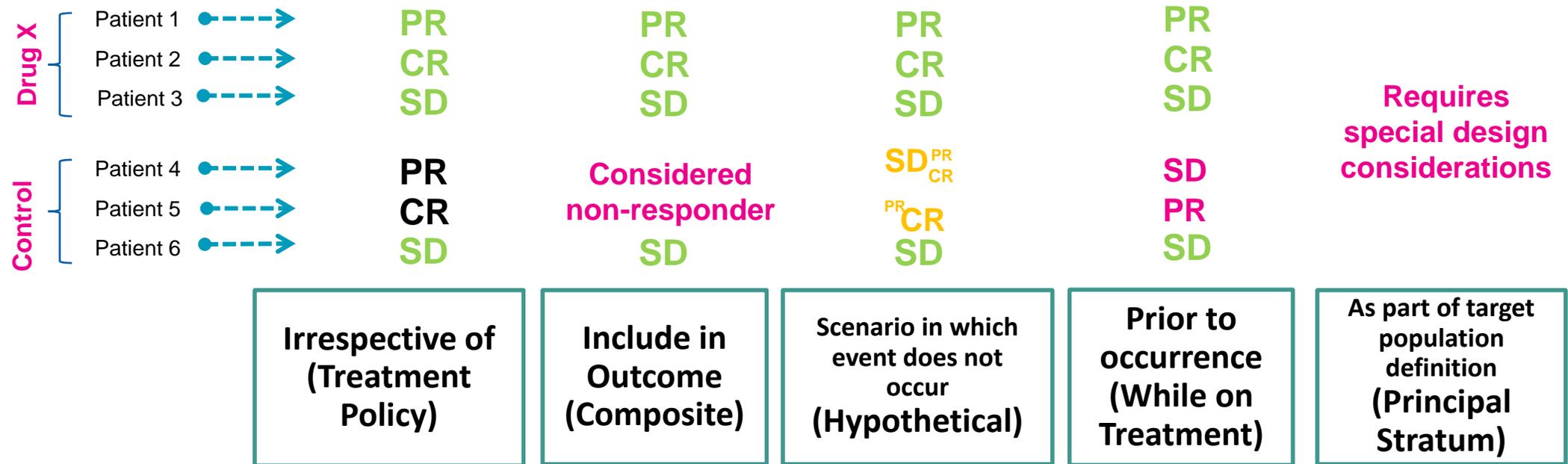|					
Drug X	Patient 1	SD	SD	PR	**PR**
	Patient 2	PR	CR	CR	**CR**
	Patient 3	SD	SD	PD	**SD**
Control	Patient 4	SD	SD		**SD**
	Patient 5	PR			**PR**
	Patient 6	SD	SD	PD	**SD**

– – On drug

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
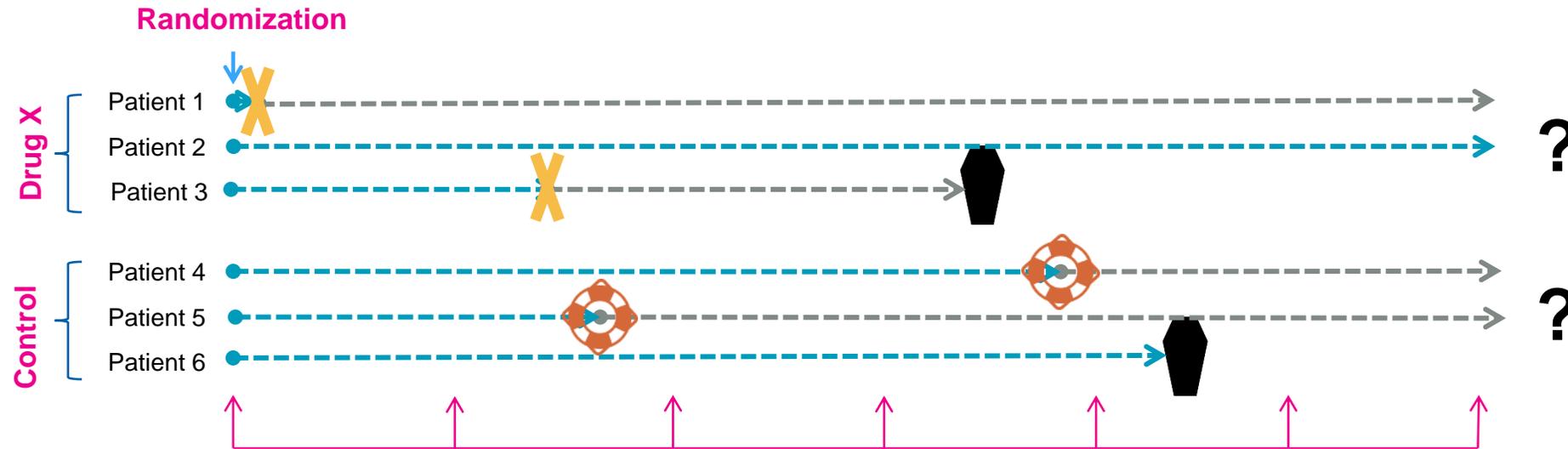
5 Strategies for Intercurrent Events

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

	Treatment Policy	Composite	Hypothetical	While on Treatment	Principal Stratum
Drug X					
Patient 1	PR	PR	PR	PR	
Patient 2	CR	CR	CR	CR	
Patient 3	SD	SD	SD	SD	
Control					**Requires special design considerations**
Patient 4	PR	Considered non-responder	SD$^{PR}_{CR}$	SD	
Patient 5	CR		^{PR}CR	PR	
Patient 6	SD	SD	SD	SD	

Irrespective of (Treatment Policy)	**Include in Outcome (Composite)**	**Scenario in which event does not occur (Hypothetical)**	**Prior to occurrence (While on Treatment)**	**As part of target population definition (Principal Stratum)**

- 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

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)**	Assumes whatever happens after randomization reflects clinical practice
Checkpoint inhibitor therapy received	**Irrespective of (Treatment Policy)**	Did not anticipate treatment switching to drugs with same mechanism of action
Question of interest	Survival benefit after prescription of Nivolumab vs Chemo regardless of whether patients take assigned treatment or receive other therapy	

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

$\mu_T - \mu_R$

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
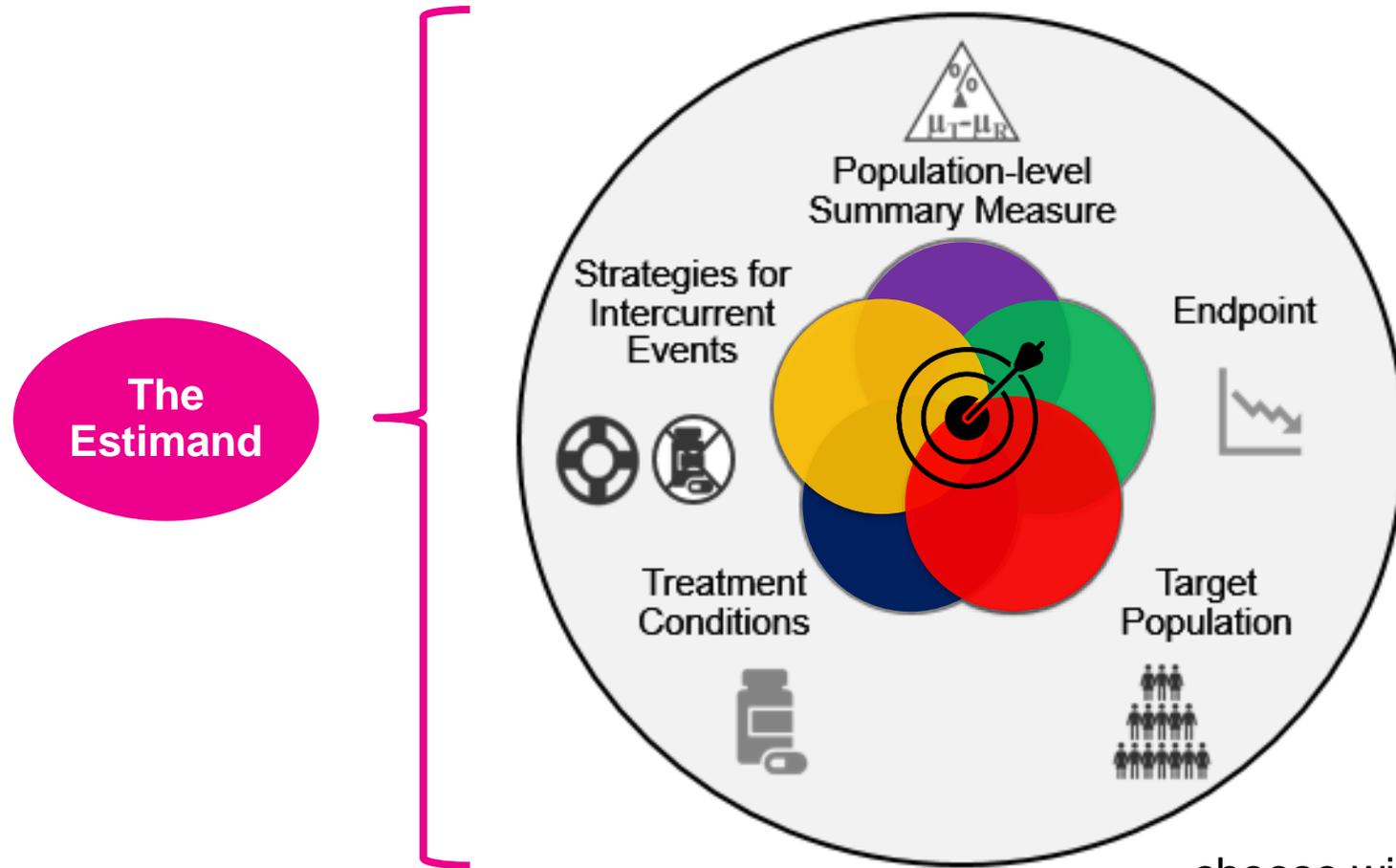
Variable

Treatment Conditions

Population-level summary

$$\mu_T - \mu_R$$

Always build your Estimand

… choose wisely and include it in the protocol!

Quiz!

Question 1

◆ What primary role is responsible for defining the estimand?

- Statistician
- Clinician
- Regulatory
- The study team

Question 2

◆ 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

Question 3

◆ 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
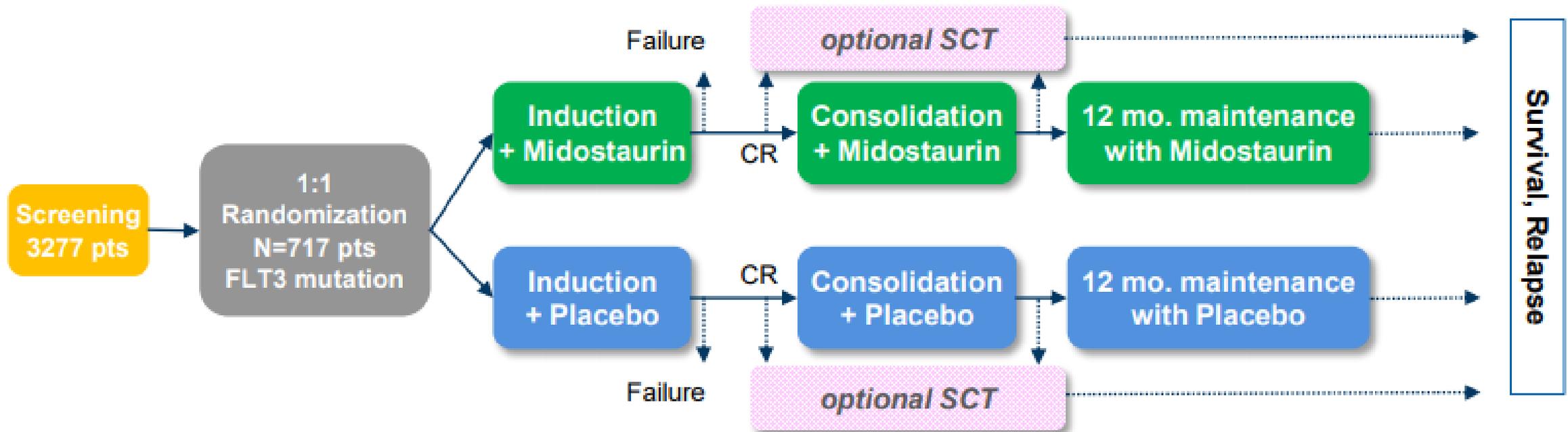
- Concomitant radiation

Case study in Hematology

Background on acute myeloid leukemia (AML) :

◆ As for other hematologic malignancies, treatments are often given in a sequence based on a certain algorithm (e.g., AML: induction, consolidation, maintenance)

◆ Stem cell transplantation (SCT) as option

- potentially curative in ~50% of patients
- associated with significant complications and with a 15-20% rate of transplant-related mortality

◆ Many new classes of drugs available recently that provide new options after treatment failure/relapse

Specific topics requiring dedicated considerations in the estimand framework

RATIFY study

- Population: newly diagnosed AML patients with a FLT-3 mutation
- Primary Objective: to determine if the addition of midostaurin to induction, consolidation, and maintenance therapy improves overall survival
- Design: Phase 3, randomized, double-blinded, placebo-controlled

 Reference: Stone (2017): Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med 377(5) 454-464

Question 4

◆ **What are the attributes of the primary estimand?
(check all that apply)**

- the sample size, n=717

- the treatment, midostaurin vs. placebo

- the endpoint, overall survival

- a description of how to handle events that occur post randomization that can preclude the observation of the endpoint or affect its interpretation (i.e., intercurrent events)

- the final p-value, p=0.009

- the population of interest, newly diagnosed AML patients with a FLT-3 mutation

- a population-level summary measure for the endpoint of interest, hazard ratio

Question 5

◆ The primary estimand in RATIFY considered overall survival regardless of receiving stem cell transplantation. What intercurrent event strategy was used for stem cell transplantation?

- Hypothetical
- Treatment policy
- Composite
- While on treatment

◆ Which intercurrent event strategy would you have used for stem cell transplantation?

- Hypothetical
- Treatment policy
- Composite
- While on treatment
- None, censor overall survival after SCT.

Question 6

◆ The benefits of estimands include (check all that apply)

- Promotes alignment between trial objectives, design, data collection, and analysis and inference

- Increases transparency over what is being measured

- Increases the number of analyses required

- Provides clear language to discuss different objectives for different stakeholders

- Strengthens the interdisciplinary dialogue at design stage

Estimands were used 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

AstraZeneca

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

Pfizer

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

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

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.)

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

Sponsors

Clinicians

Clinical Trial Design & Conduct

Statisticians

Other Disciplines
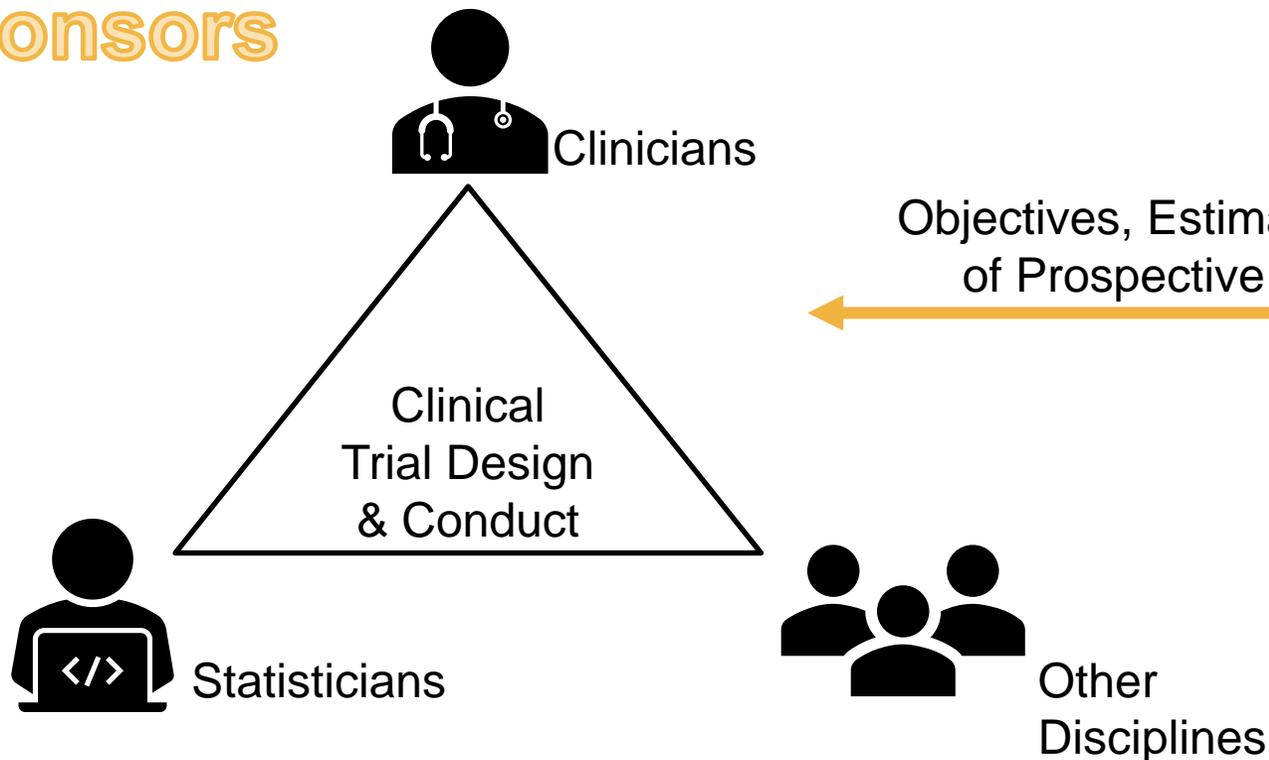
Objectives, Estimands and Design of Prospective Clinical Trials

Regulators

Ethics Committees

The Estimands Academy for Trial Teams
"Bringing estimands to *life* through real case studies"

Two webinars coming soon:

- Respiratory case study
- Using estimands in trials developing COVID vaccines