

# Estimand framework – do you know the research question?

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Biostatistics**

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# Good research starts with a question

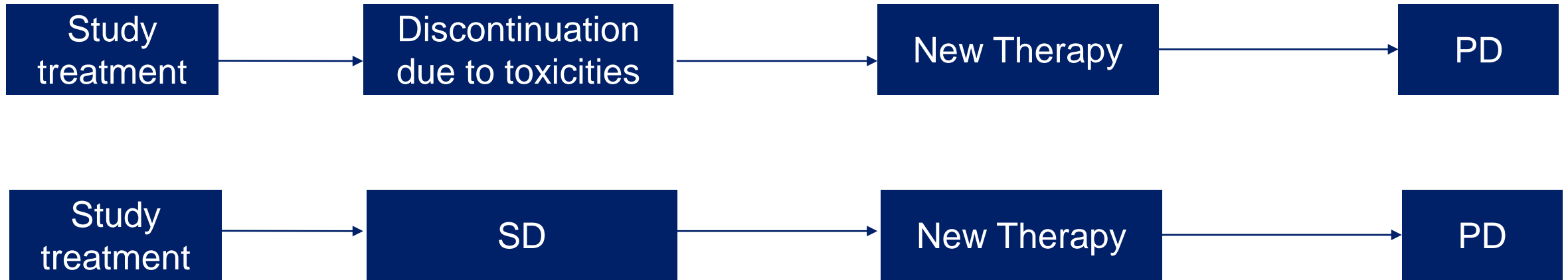


Does the new treatment prolong time to progression or death compared to SoC?

Is it a well-defined question?

R: Randomization SoC: Standard of Care, PFS: Progression-free Survival

# Patient journeys

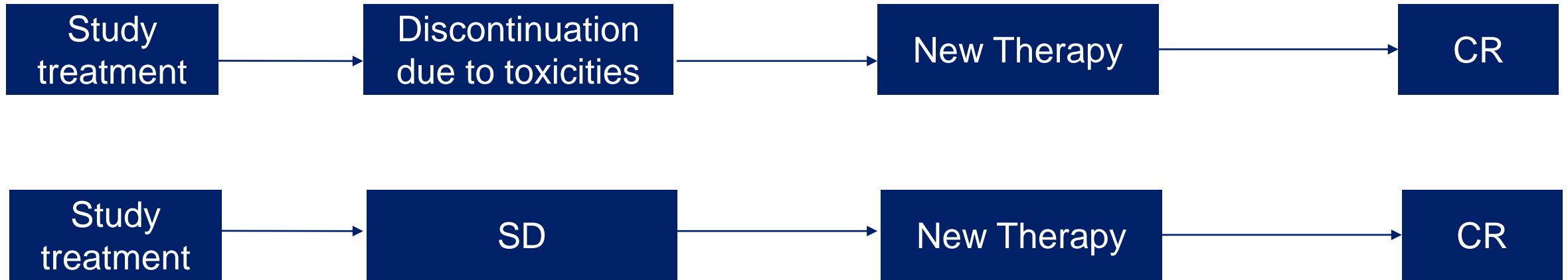


PD = PFS event ?

Polarix trial: yes

Zuma-7 trial: no

# Patient journeys



CR = PFS time ?

Polarix trial: yes

Zuma-7 trial: no

# Two typical PFS definitions

	PFS definition #1	PFS definition #2
Hidden somewhere in the SAP	Consider data after new therapy	Censor in K-M analysis prior to start of new therapy
Polarix trial	Primary analysis: HR 0.73, p=0.0177	FDA request: HR 0.77, p=0.0567
Not mentioned anywhere: implied scientific question	What is the time to PD or death regardless of new therapies? (i.e. combined effect of study treatment and subsequent therapies until PD or death)	What is the time to PD or death if new therapies are not available? (hypothetical world)

Different questions!

SAP: Statistical Analysis Plan; K-M: Kaplan-Meier

# Alternative PFS definition in Polar Bear trial

PFS = time to PD, death or lack of response



SD (lack of response) = PFS event

Assessing the time to PD, death or lack of response

Different question compared to time to PD or death!

Based on clinicaltrials.gov

# The past

No clarity on the scientific question

Analysis conventions (e.g. censoring) at the center of discussion

Misalignment between stakeholders

Risk of misinterpreting trial results

Comparisons across trials not possible



# Problem recognized by regulators and pharmaceutical industry

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)**

Estimand framework introduced by ICH in 2019

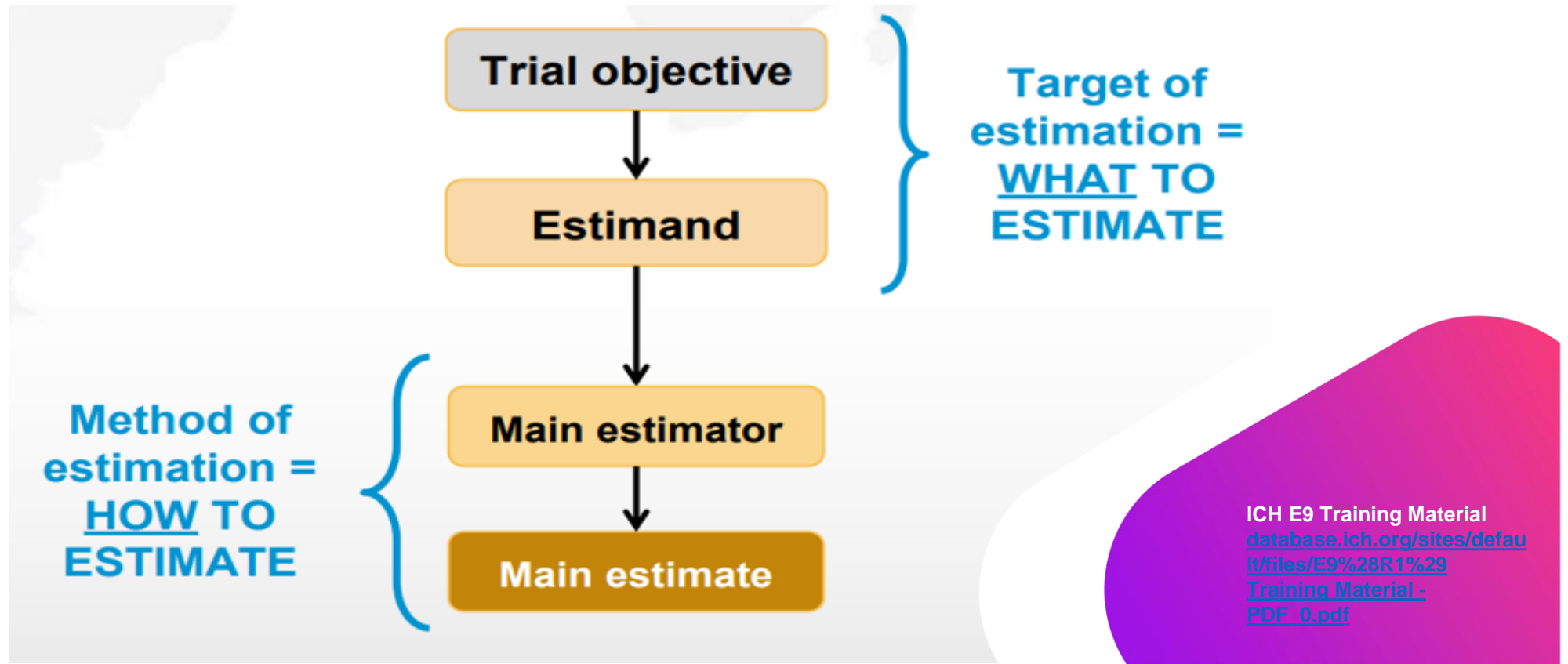
Adopted by all major regulators

Implemented in protocol templates by the industry



# Aligning trial objectives and analysis

Start with a question/objective

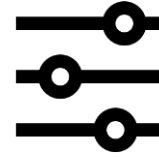


# 5 attributes of an estimand



## Population

Patients targeted by the question of interest



## Intercurrent events

Clinical events after randomization impacting the interpretation of the treatment effect



## Treatment

Treatment condition of interest (drugs, combinations, treatment sequences etc)



## Population-level summary

Provides a basis for comparison between treatments



## Variable (or endpoint)

To be obtained for each patient in order to address the question of interest

# Two estimands in Polarix trial

	Estimand #1	Estimand #2
Population	Patients with newly diagnosed DLBCL	
Variable	PFS: time to PD or death	
Summary measure	Hazard ratio	
Intercurrent event: New Therapy	PDs and deaths after start of new therapy are considered as PFS events (treatment policy)	PDs and deaths after start of new therapy are not considered as PFS events (hypothetical)
Treatment		

# Two estimands in Polaris trial

	Estimand #1	Estimand #2
Population	Patients with newly diagnosed DLBCL	
Variable	PFS: time to PD or death	
Summary measure	Hazard ratio	
Intercurrent event: New Therapy	PDs and deaths after start of new therapy are considered as PFS events (treatment policy)	PDs and deaths after start of new therapy are not considered as PFS events (hypothetical)
Treatment	Pola-R-CHP + subsequent therapies vs R-CHOP + subsequent therapies until PD or death	Pola-R-CHP vs R-CHOP
Scientific question	What is the time to PD or death regardless of new therapies? (i.e. combined effect of study treatment and subsequent therapies!)	What is the time to PD or death if new therapies are not available?



# Event-free Survival (EFS)

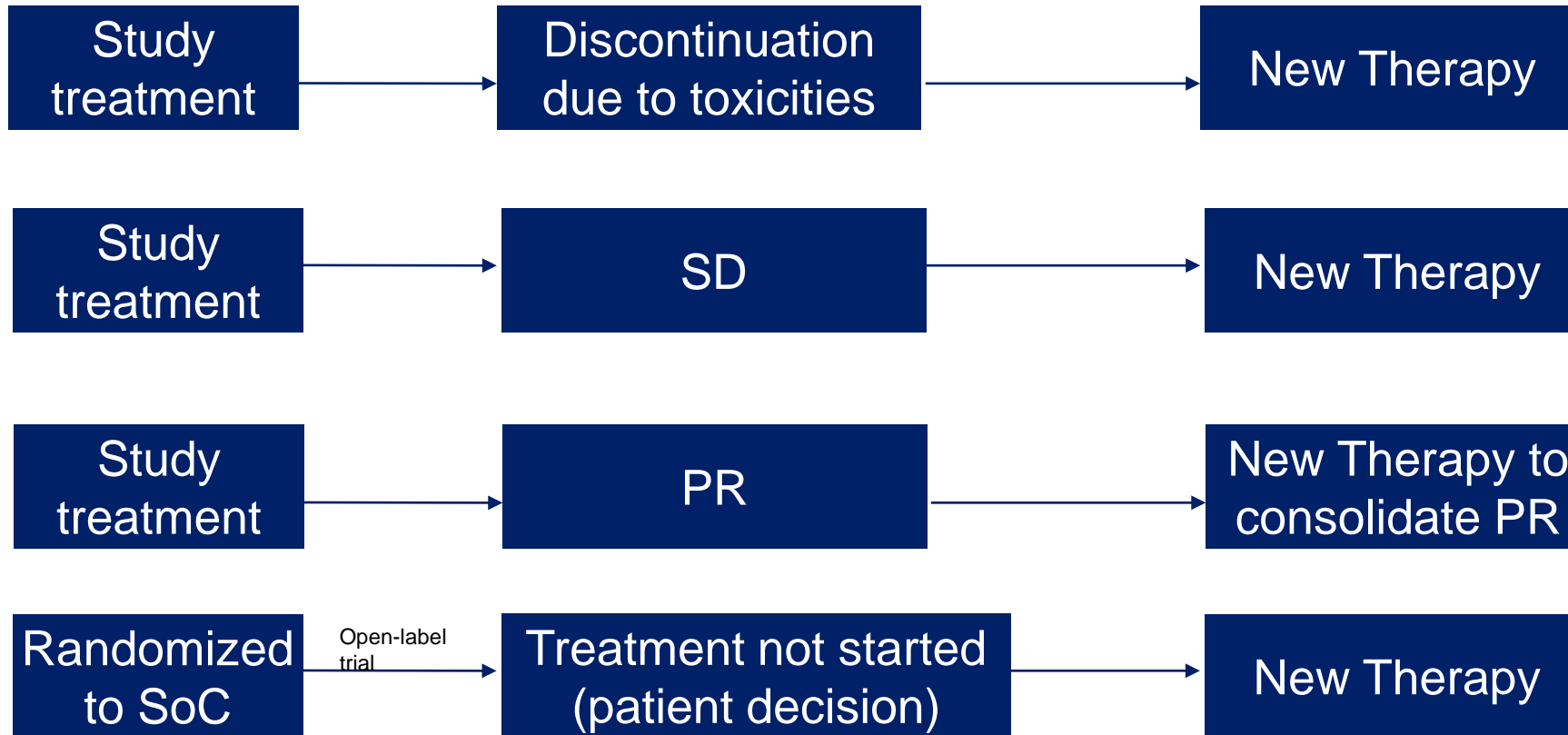
In DLBCL trials EFS used as a primary or secondary endpoint often considering start of new therapy and/or lack of response as event (composite)

Delaying start of new therapy can be a meaningful treatment goal

But is it always informative with regard to the efficacy of the assigned therapy?

# EFS: counting new therapy as event

## Always bad outcome for patients?



SoC: Standard of Care, PR: Partial Response, SD: Stable Disease

# Variety of EFS definitions

1L DLBCL trial	EFS defined as time from randomization to ...
Polarix trial, Pola-R-CHP vs R-CHOP	EFSeff (key secondary endpoint): disease progression, death, <b>primary efficacy reason</b> determined by the investigator other than disease progression/relapse, <b>that leads to initiation of start of new antineoplastic therapy</b> ; if biopsy is obtained after treatment completion, and is positive for residual disease
Zuma-23 trial, Axicabtagene Ciloleucel vs R-CHOP or DA-EPOCH-R	EFS (primary endpoint): disease progression, death, <b>initiation of any non-protocol specified subsequent new lymphoma therapy</b> for the treatment of residual disease or biopsy-proven residual disease at the Month 6 disease assessment or later, regardless of whether subsequent new lymphoma therapy is initiated or not

Different questions requiring different data to be collected!

Based on Tilly et al (2022) and clinicaltrials.gov

# Value of the framework recognized by regulators



26 June 2020  
EMA/158330/2020 Rev. 1  
Committee for Human Medicinal Products (CHMP)

Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials

STATISTICS IN BIOPHARMACEUTICAL RESEARCH  
2020, VOL. 12, NO. 4, 427–437  
<https://doi.org/10.1080/19466315.2020.1785543>



## Assessing the Impact of COVID-19 on the Clinical Trial Objective and Analysis of Oncology Clinical Trials—Application of the Estimand Framework

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EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

13 April 2022  
EMA/214249/2022  
Biostatistics Working Party

Points to consider on the impact of the war in Ukraine on methodological aspects of ongoing clinical trials



# Estimand thinking in lymphoma



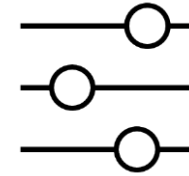
Lack of clarity and consistency in endpoint definitions in lymphoma trials

Not all endpoint rules seem to be patient-relevant!



Need to define the questions of interest and corresponding endpoints

Different stakeholders may have different questions dependent on the type of therapy and disease subtype



Assessing endpoint rules across a range of plausible patient journeys can facilitate the dialogue

Manuscript «Endpoints in clinical trials in diffuse large-B cell lymphoma – time for more dialogue?» submitted in collaboration with patient advocates

# The future with estimand framework

Patient journeys at the center of discussion - common language for all stakeholders

Transparency on the questions of interest

Clarity when interpreting and contextualizing trial results



# Acknowledgements

Many colleagues at Novartis who shaped my thinking

Kaspar Rufibach (Roche) and members of the industry working group on estimands in oncology ([www.oncoestimand.org](http://www.oncoestimand.org))

Co-authors of the submitted manuscript «Endpoints in clinical trials in diffuse large-B cell lymphoma – time for more dialogue?»



“The art and science of asking questions is the source of all knowledge.”

Thomas Berger  
American Novelist