Estimand framework – do you know the research question?

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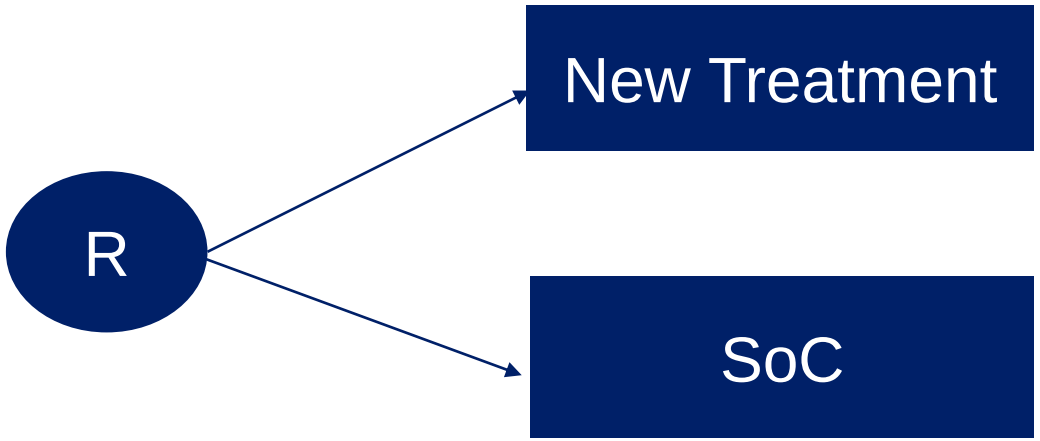
Good research starts with a question



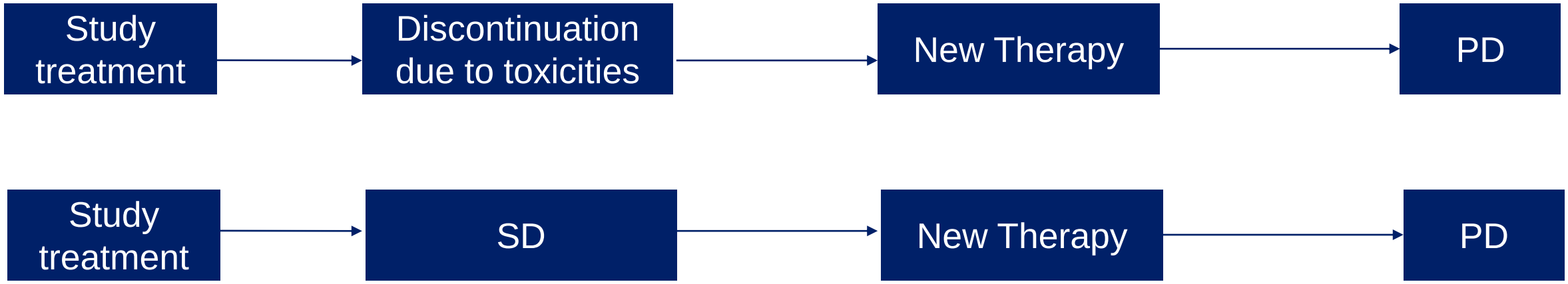
Endpoint: PFS

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

Is it a well-defined question?

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

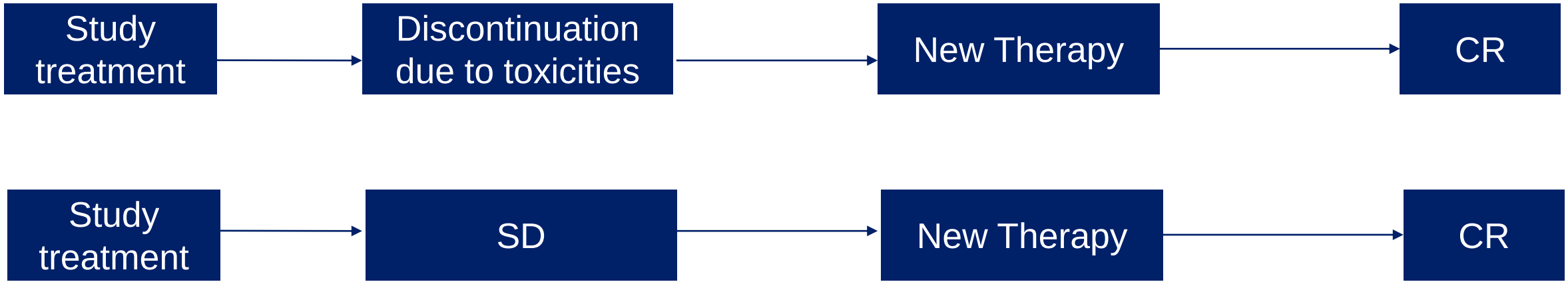
Patient journeys



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 anywere: 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 clinicalrials.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

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)

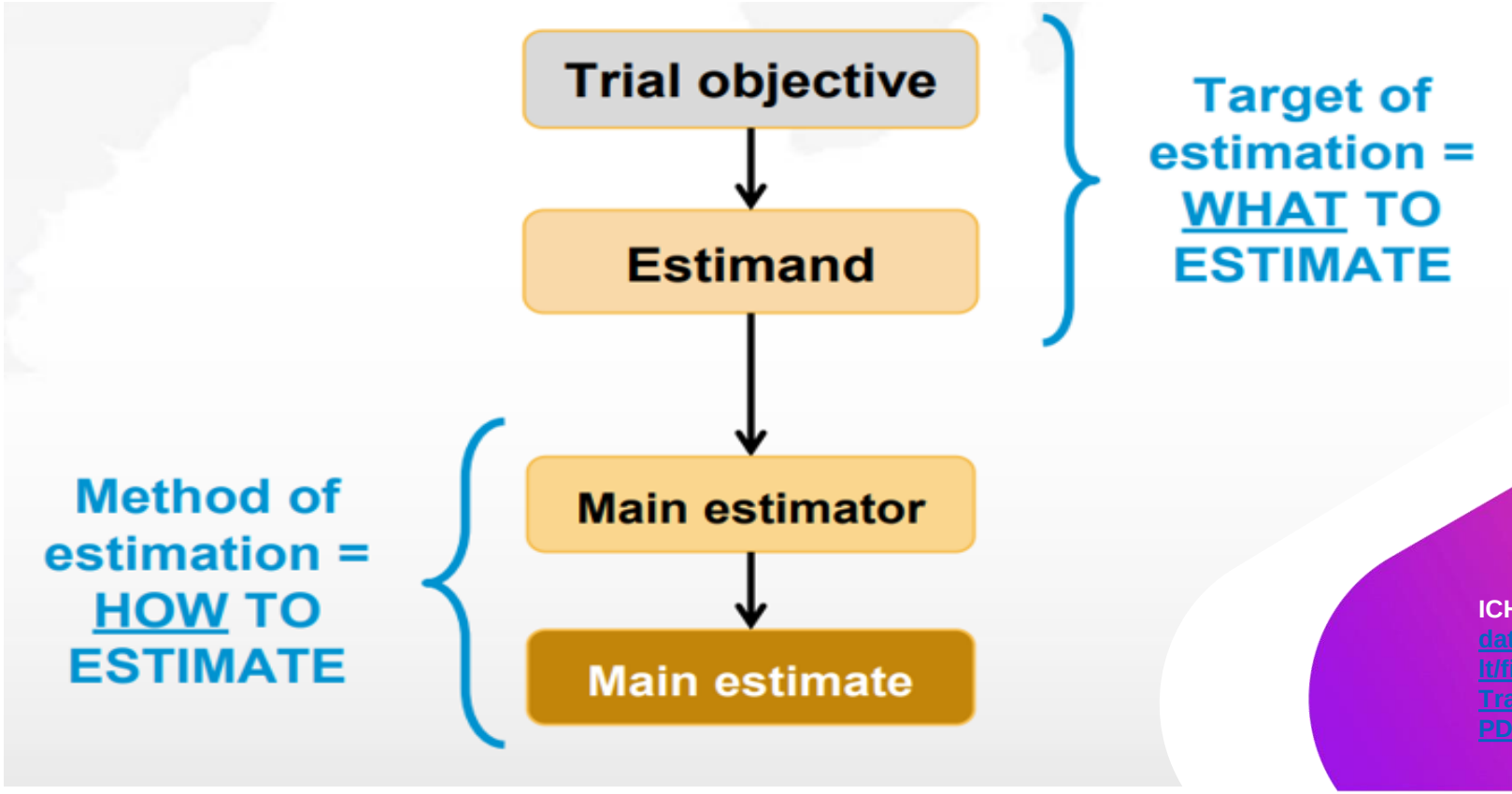
Estimand framework introduced by ICH in 2019

Adopted by all major regulators

Implemented in protocol templates by the industry

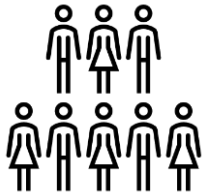
Aligning trial objectives and analysis

Start with a question/objective



ICH E9 Training Material
database.ich.org/sites/default/files/E9%28R1%29 Training Material - PDF_0.pdf

5 attributes of an estimand



Population

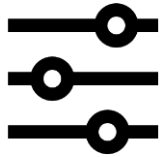
Patients targeted by the question of interest

Treatment

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

Variable (or endpoint)

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



Intercurrent events

Clinical events after randomization impacting the interpretation of the treatment effect

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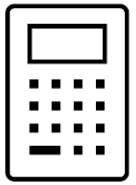

Population-level summary

Provides a basis for comparison between treatments

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 Polarix trial

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Population	Patients with newly diagnosed DLBCL	
Variable	PFS: time to PD or death	
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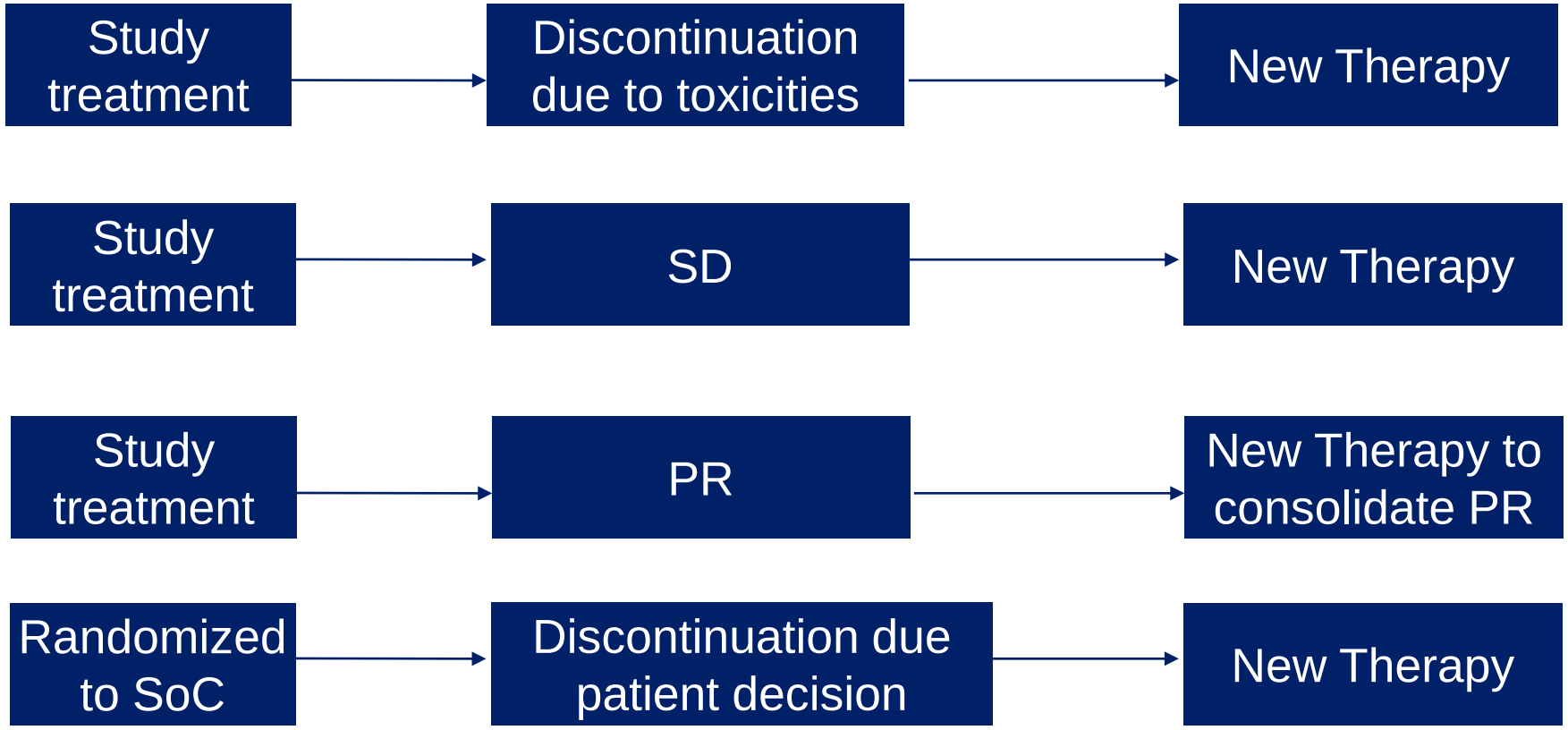
Intercurrent event: New Therapy	PDs and deaths after start of new therapy are considered as PFS events (treatment policy)	PDs and deaths after start of new therapy are not considered as PFS events (hypothetical)
Treatment	Pola-R-CHP + subsequent therapies vs R-CHOP + subsequent therapies until PD or death	Pola-R-CHP vs R-CHOP
Scientific question	What is the time to PD or death regardless of new therapies?	What is the time to PD or death if new therapies are not available?

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, primary efficacy reason determined by the investigator other than disease progression/relapse, that leads to initiation of start of new antineoplastic therapy; 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, initiation of any non-protocol specified subsequent new lymphoma therapy 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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

Taylor & Francis
Taylor & Francis Group

Check for updates

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

Evgeny Degtyarev[*a], Kaspar Rufibach[*b], Yue Shentu[*c], Godwin Yung[*d], Michelle Casey[e], Stefan Englert[f], Feng Liu[g], Yi Liu[h], Oliver Sailer[i], Jonathan Siegel[j], Steven Sun[k], Rui Tang[l], Jiangxiu Zhou[m], and on behalf of the Industry Working Group on Estimands in Oncology[†]

[a]Novartis Pharma AG, Basel, Switzerland; [b]F. Hoffmann-La Roche, Basel, Switzerland; [c]Merck & Co., Inc., Rahway, NJ; [d]Takeda Pharmaceuticals, Cambridge, MA; [e]Pfizer, Collegeville, PA; [f]AbbVie Deutschland GmbH & Co KG, Ludwigshafen, Germany; [g]AstraZeneca, Gaithersburg, MD; [h]Nektar Therapeutics, San Francisco, CA; [i]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; [j]Bayer US Inc., Whippany, NJ; [k]Janssen R&D, Raritan, NJ; [l]Servier Pharmaceuticals, Boston, MA; [m]GlaxoSmithKline, Collegeville, PA

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

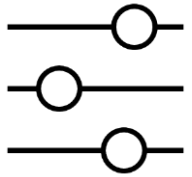
Estimand thinking in lymphoma

Lack of clarity and consistency in PFS, EFS and PRO 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)

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