Some challenges with implementing estimands in real life

Kaspar Rufibach
Methods, Collaboration, and Outreach Group, Roche Data Sciences, Basel
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Acknowledgments

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- by Kaspar Rufibach and **Evgeny Degtyarev (Novartis)**.
- Sections on switching and hypothetical estimands had initially been prepared by Evgeny.

Acknowledgments

We borrowed slides or were inspired by

- **Hans-Jochen Weber** & **Renaud Capdeville**,
- **Björn Bornkamp**.

All our colleagues of the **industry working group on estimands in oncology**.

Regulatory colleagues around the world for regular discussion, their input, and feedback.

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Sheiner (1991)

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Roche quantitative scientist

If you do not know how to ask the right question, you discover nothing.

W.E. Deming, American Statistician

Agenda

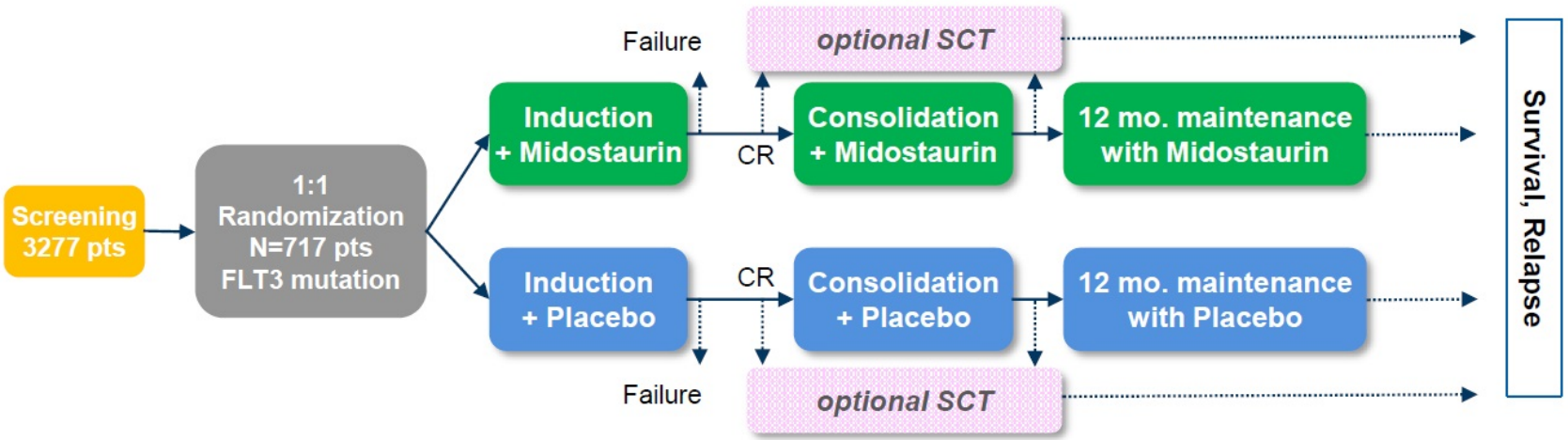
1. Case study: hematology
2. Hypothetical strategy to address ICEs: application to Covid-19
3. Case study: treatment switching
4. Estimation of average causal effect
5. Subgroups by post-randomization event - principal stratification
6. Estimation of principal effects
7. Impact of ICH E9(R1) and conclusions
8. Resources

Agenda

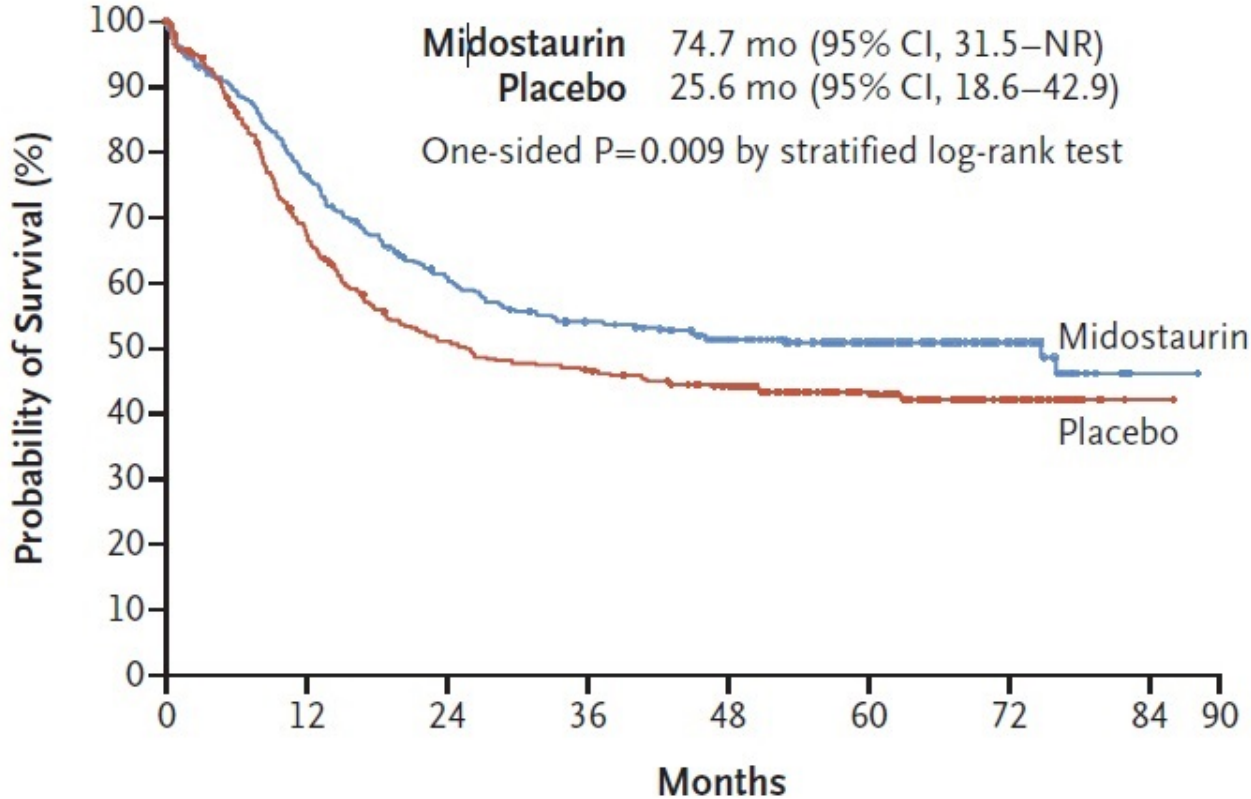
Case study: hematology

Complex treatment strategies in hematology

Ratify trial, Stone et al. (2017).



- **Randomized, phase III** double-blind clinical trial.
- **Population**: newly diagnosed AML with a FLT 3 mutation.
- **Comparison**: after completion of primary therapy: Midostaurin vs. placebo.
- **Primary endpoint**: OS.
- **Key secondary endpoint**: EFS.



No. at Risk

Midostaurin	360	269	208	181	151	97	37	1
Placebo	357	221	163	147	129	80	30	1

OS was significantly longer in the midostaurin group than in the placebo group, as was EFS. [...] In both the primary analysis and an analysis in which **data for patients who underwent transplantation were censored**, *the benefit of midostaurin was consistent across all FLT3 subtypes.*

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Completely different clinical questions!

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- **SmPC**: In combination with **induction** and **consolidation**, and for patients in complete response followed by single agent **maintenance** therapy.
- **USPI**: In combination with standard **induction** and **consolidation**.

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- Maintenance: Despite explicit inclusion in trial objective $\Rightarrow$ **inconsistently included in EMA and FDA labels**.

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Summary measure: hazard ratio.

Complex (multiphase) strategies:

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Cure?

What do these findings have in common?

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Clear formulation of
clinical trial objective is key.

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MAIN PAPER

WIL

Estimands in hematologic oncology trials

Steven Sun[1] | Hans-Jochen Weber[2] | Emily Butler[3] | Kaspar Rufibach[4] | Satrajit Roychoudhury[5]

Sun et al. (2021):

- Three case studies.
- Categorization and discussion of sensitivity and supplementary analyses.
- Templates for protocol and SAP.

Agenda

Hypothetical strategy to address ICEs: application to Covid-19

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Censoring:

- **Estimation** method.
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- Do not make it part of estimand definition!

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Framework useful to discuss **impact of COVID-19 on ongoing and future trials.**

Assessing impact of COVID-19 on estimand

VARIABLE

The variable (or endpoint) to be obtained for each patient.
Q: Does the current endpoint reflect the treatment effect in the original scientific objective?

POPULATION

The population of patients targeted by the clinical question.
Q: Are the enrolled patients representative of the target population?

INTERCURRENT EVENTS (ICEs)

Other ICEs not already addressed by treatment, population and variable, and how they are handled.
Q: Can the original clinical trial objective be addressed without defining new strategies for ICEs related to COVID-19? (e.g. apply pre-specified rules for discontinuations to discontinuations due to COVID-19)

TREATMENT

The treatment condition of interest.
Q: Are the treatment conditions (e.g. non-compliance, drug discontinuation, subsequent therapy) representative of what would have been administered pre-COVID-19?

SUMMARY

A population-level summary for the variable which provides a basis for treatment comparison.
Q: Is the summary measure still interpretable?

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Trial objectives: relate to world without COVID-19 pandemic (?)

Intercurrent events primarily caused by disruption of healthcare system or patients' desire to minimize traveling independently of disease or treatment: **hypothetical strategy reasonable**.

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War in Ukraine – similar question.

Health authority guidances for both.

Agenda

Case study: treatment switching

Good old days: Herceptin

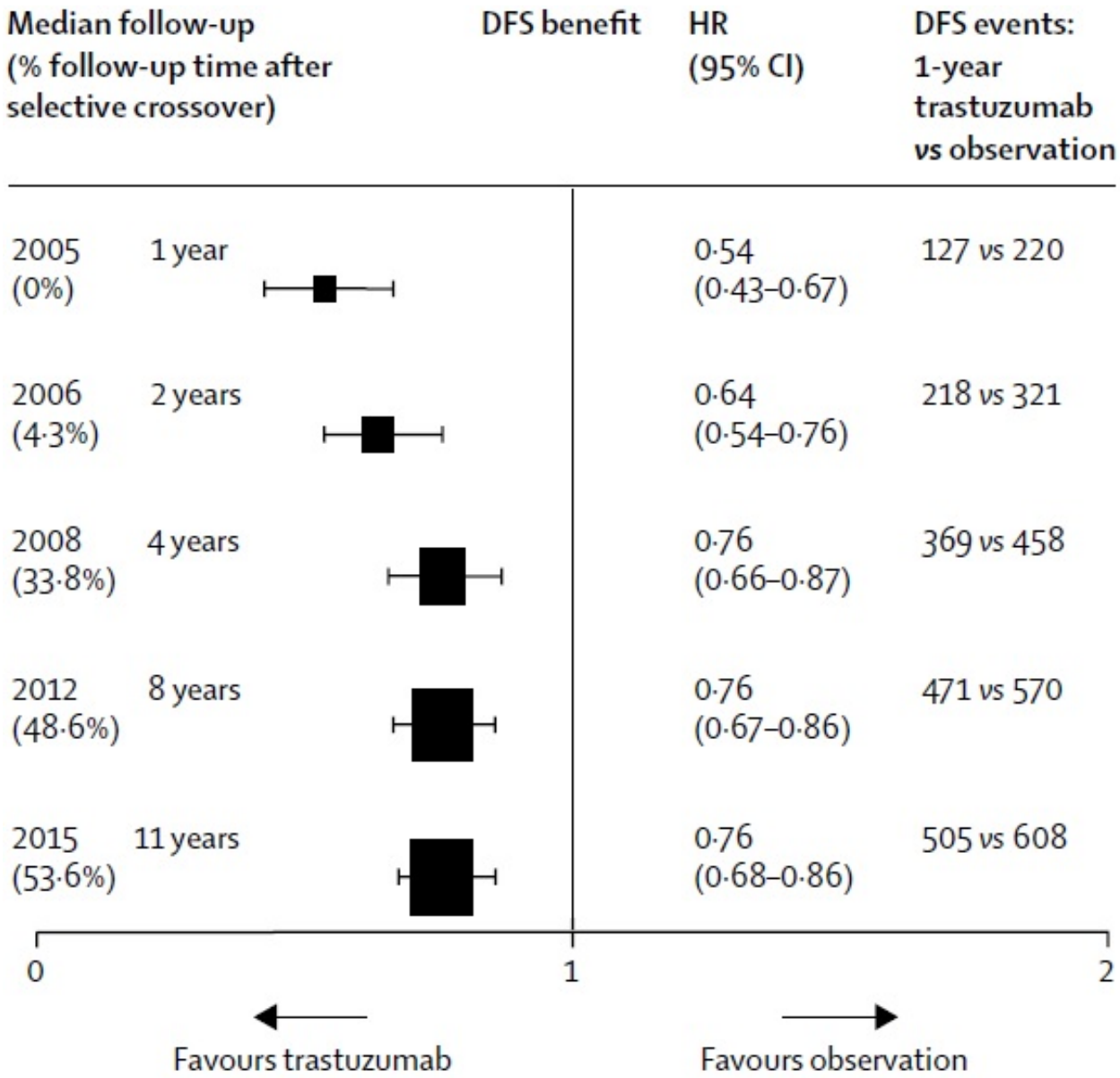
HERA

- **Population**: HER2+ early breast cancer patients.
- **Primary therapy**: surgery, chemotherapy, or radiotherapy as indicated.
- **Comparison**: after completion of primary therapy: trastuzumab vs. observation.
- **Randomized, phase III** clinical trial.
- Primary endpoint: investigator-assessed **disease-free survival**.

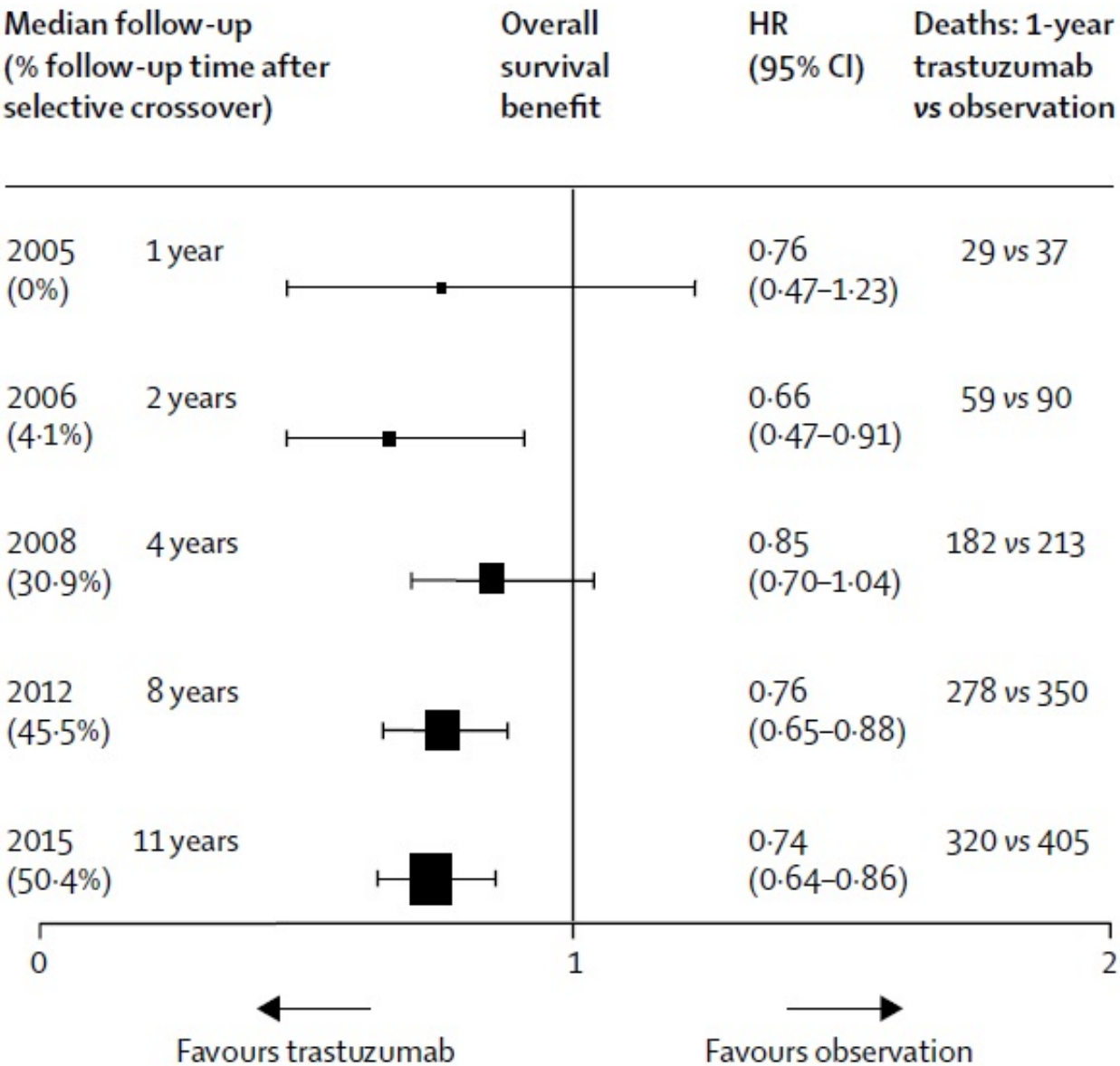
Piccart-Gebhart and Procter (2005):

- Trial stopped **early** at planned interim analysis (347 events).
- All control patients without prior disease recurrence allowed to **cross-over to trastuzumab** $\Rightarrow$ 52% did so.

Primary endpoint DFS in HERA over time



Overall survival in HERA over time



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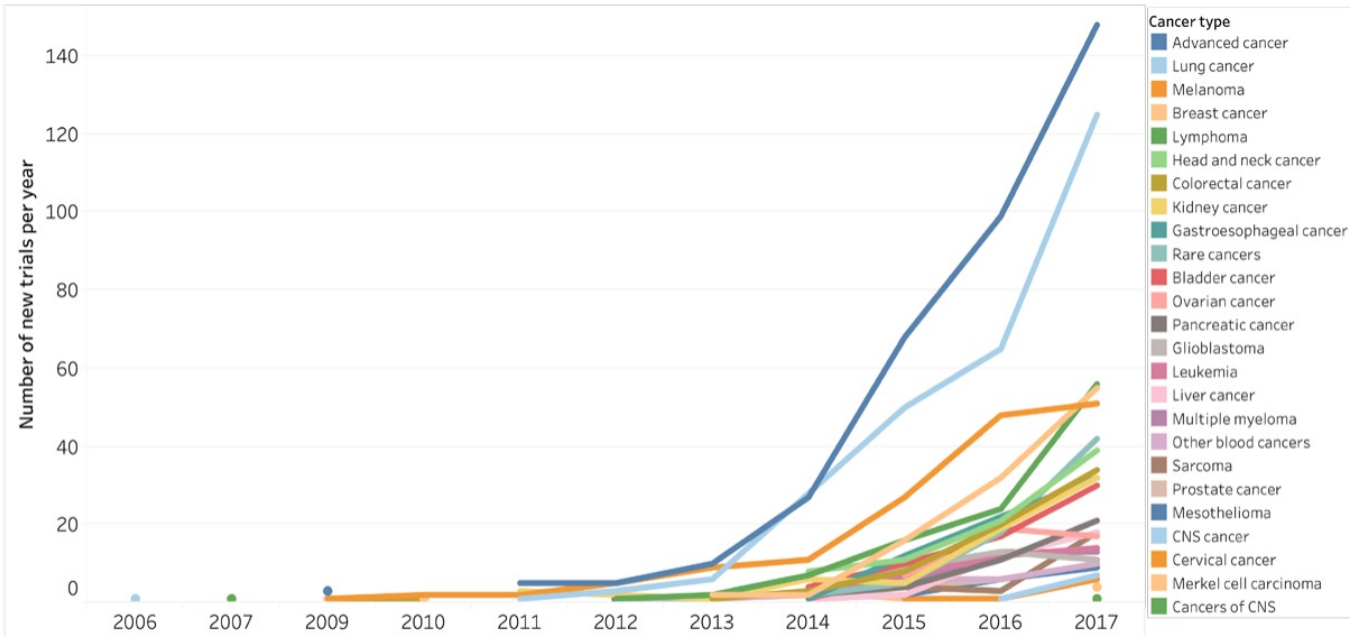
Treatment policy estimand interpretable.

Oncology landscape has changed!

Clinical trials with anti-PD1/PDL1 agents

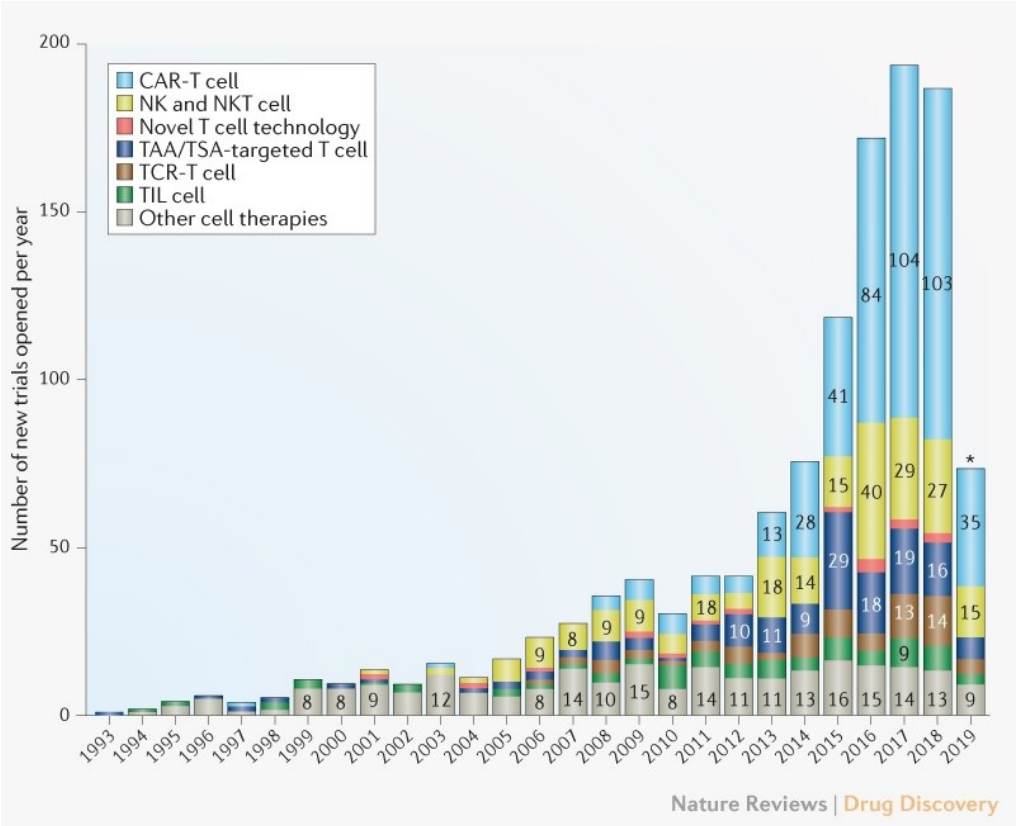


1 in 2006, **1502** in Sep 2017, **2250** in Sep 2018, **2975** in Sep 2019.

Tang et al. (2018)

`https://www.cancerresearch.org/scientists/immuno-oncology-landscape/pd-1-pd-l1-landscape`.

CAR-T trials



13 in 2013, >**100** in 2017.

Yu et al. (2018).

Great for patients!

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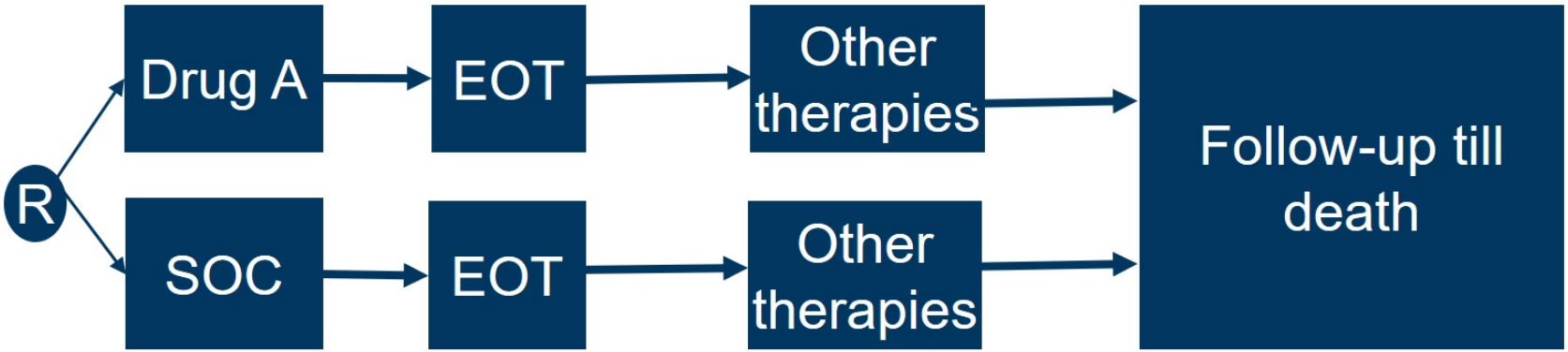
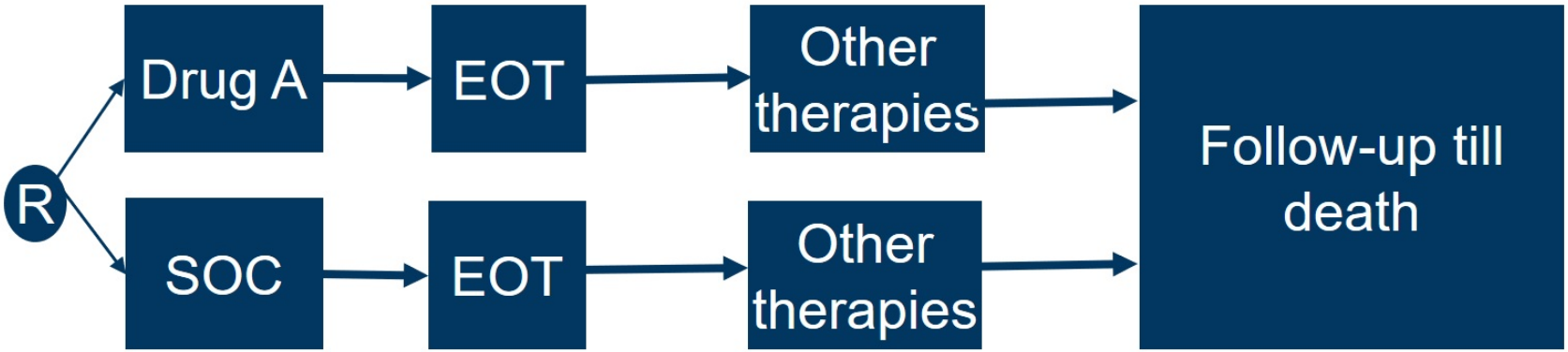
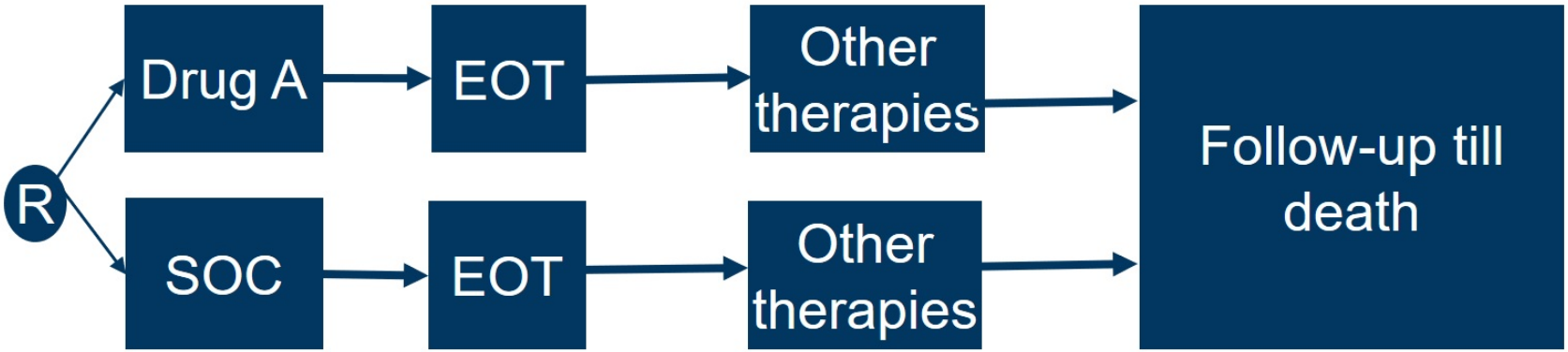
But what does it mean for clinical trials?


R
Drug A
SOC
EOT
EOT
Other therapies
Other therapies
Follow-up till death



Typical OS definition:



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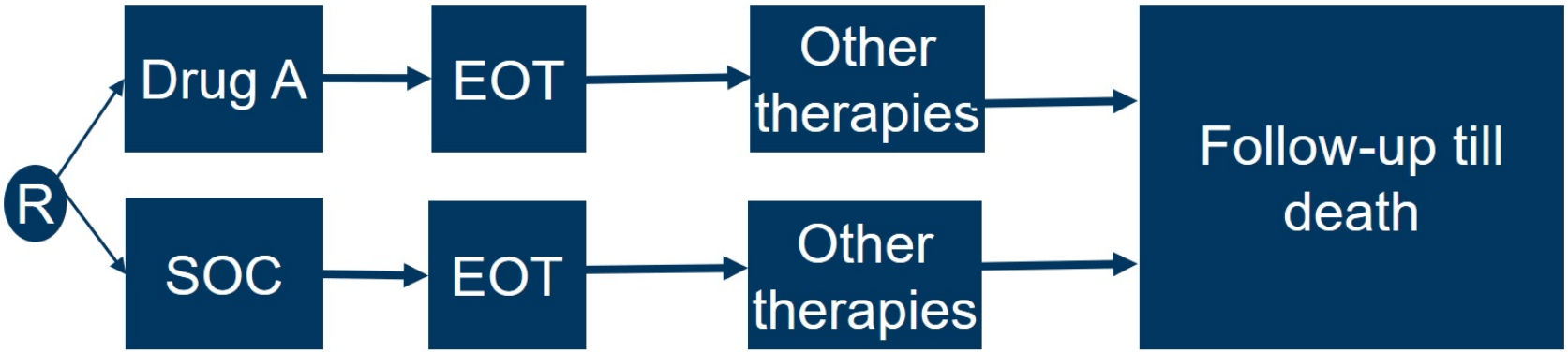

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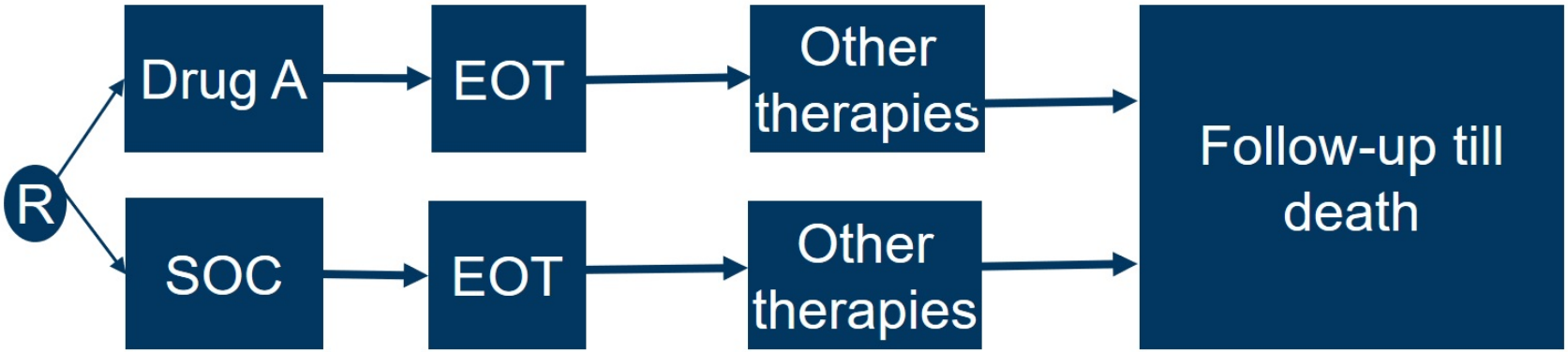

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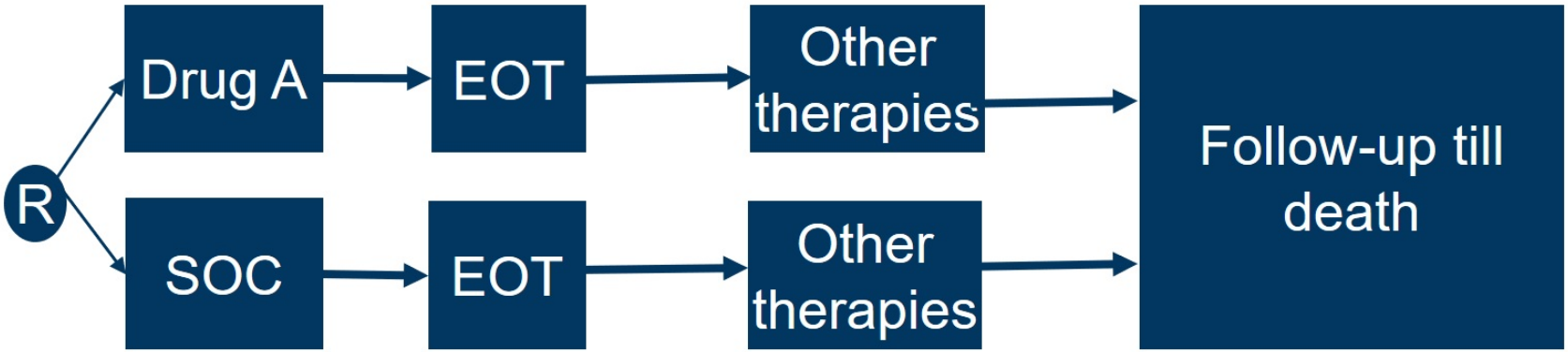

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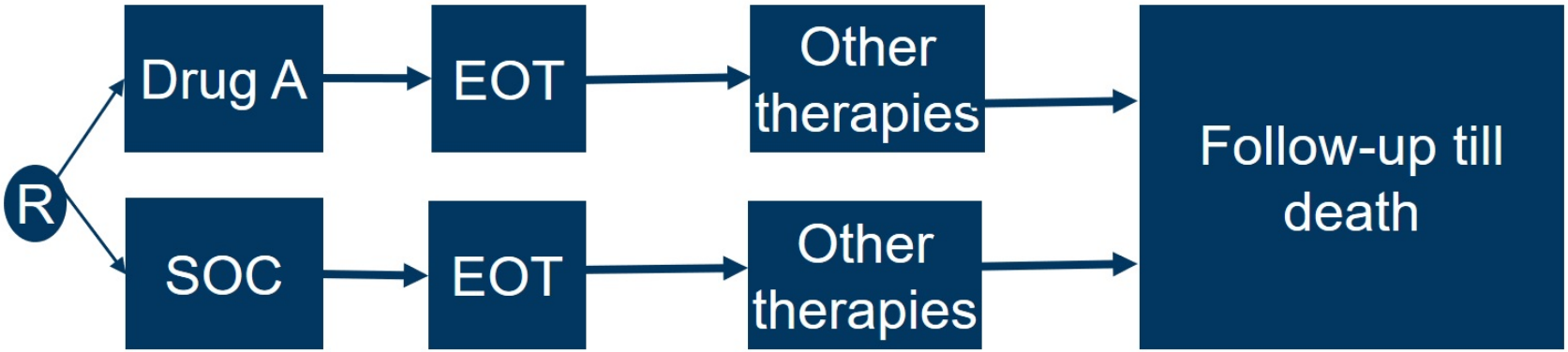

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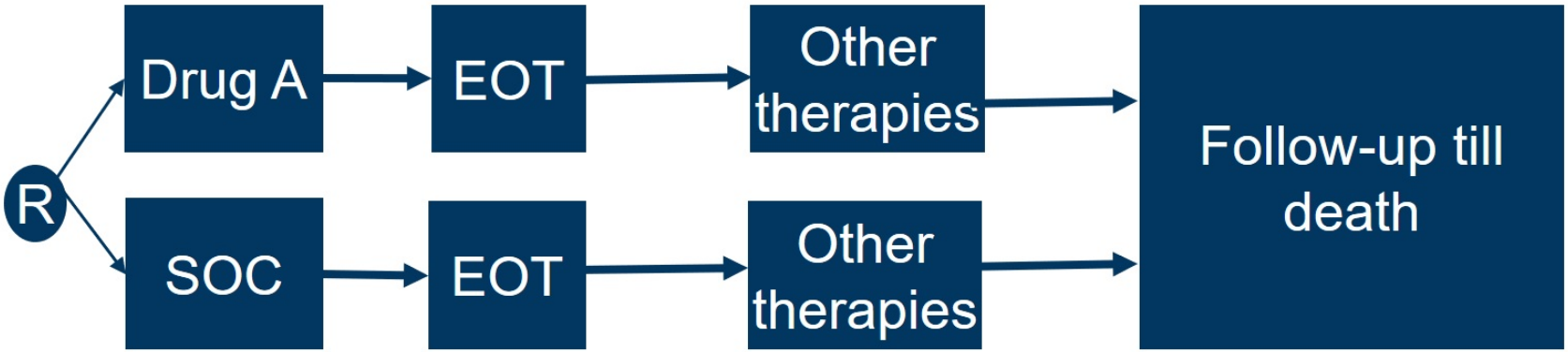
  - If experimental drug works $\Rightarrow$ less switchers.



Typical OS definition:

- Time from randomization to death **regardless of patient's journey**.
- **Treatment policy** for every intercurrent event (crossover, new therapy, etc.).
- Balance in subsequent therapies generally not expected:
  - Physician choose subsequent therapy in light of previously administered therapies.
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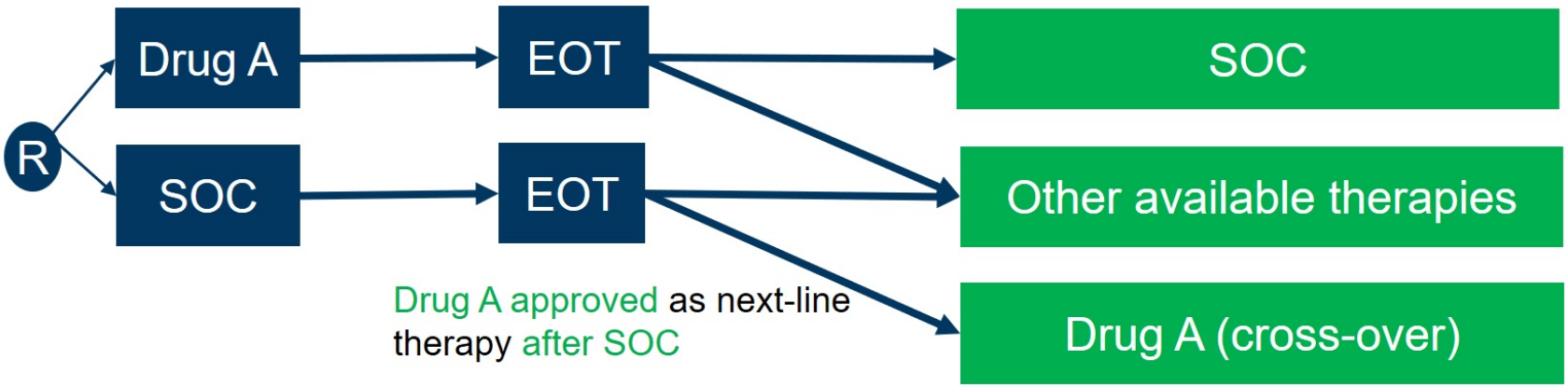
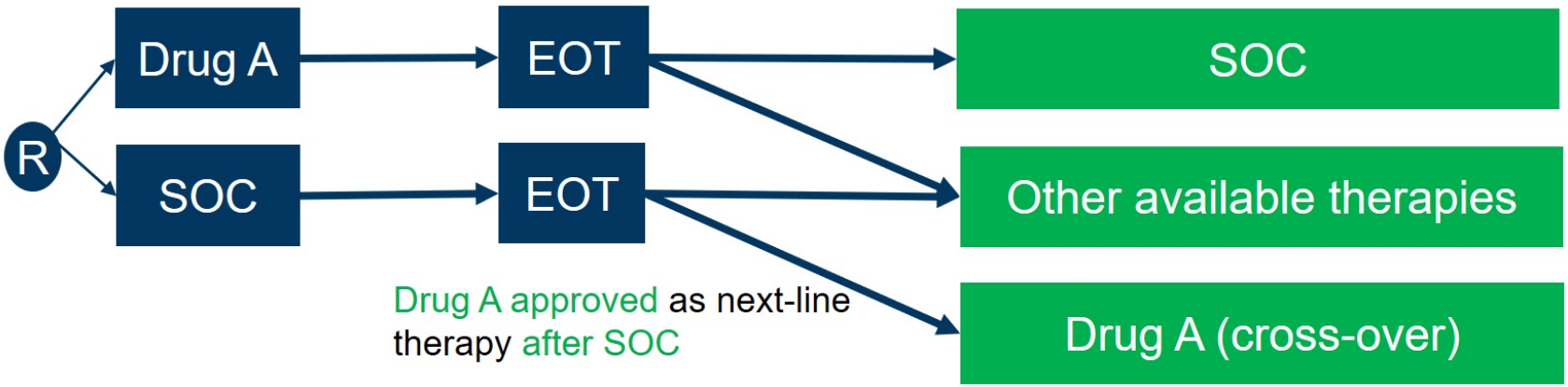
Treatment policy OS estimand **interpretable** if subsequent therapy after EOT reflects **clinical practice**.


Drug A
EOT
SOC
R
SOC
EOT
Other available therapies
Drug A approved as next-line therapy after SOC
Drug A (cross-over)



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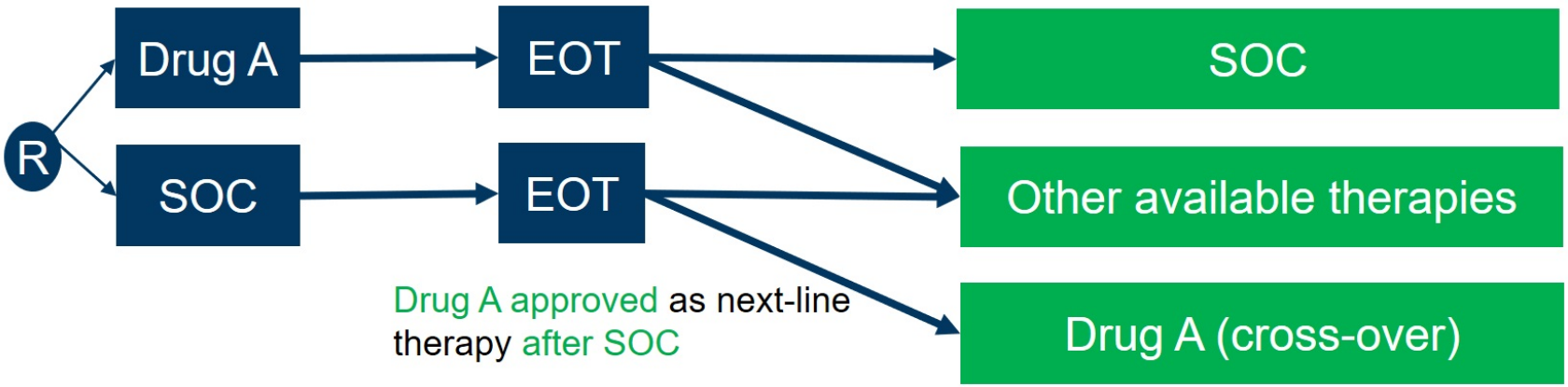

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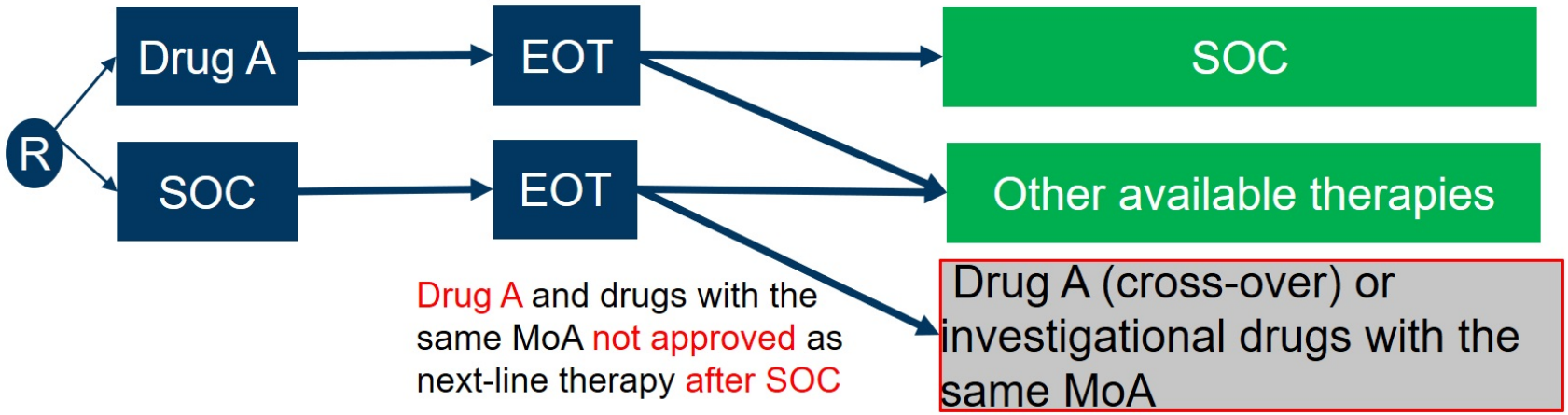
R
Drug A
SOC
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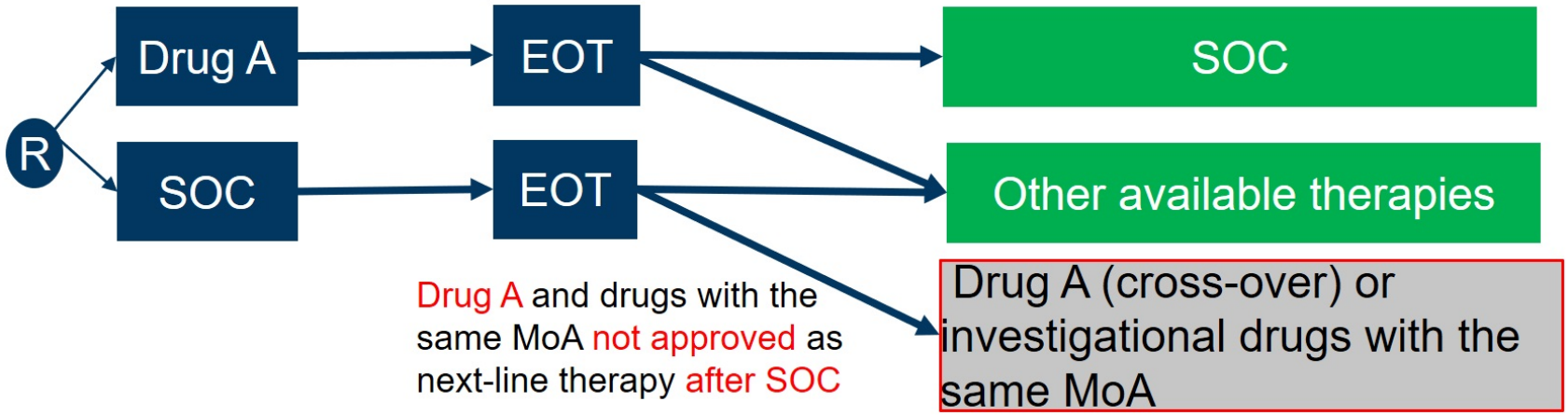
Other available therapies
Drug A (cross-over) or investigational drugs with the same MoA
Drug A and drugs with the same MoA not approved as next-line therapy after SOC



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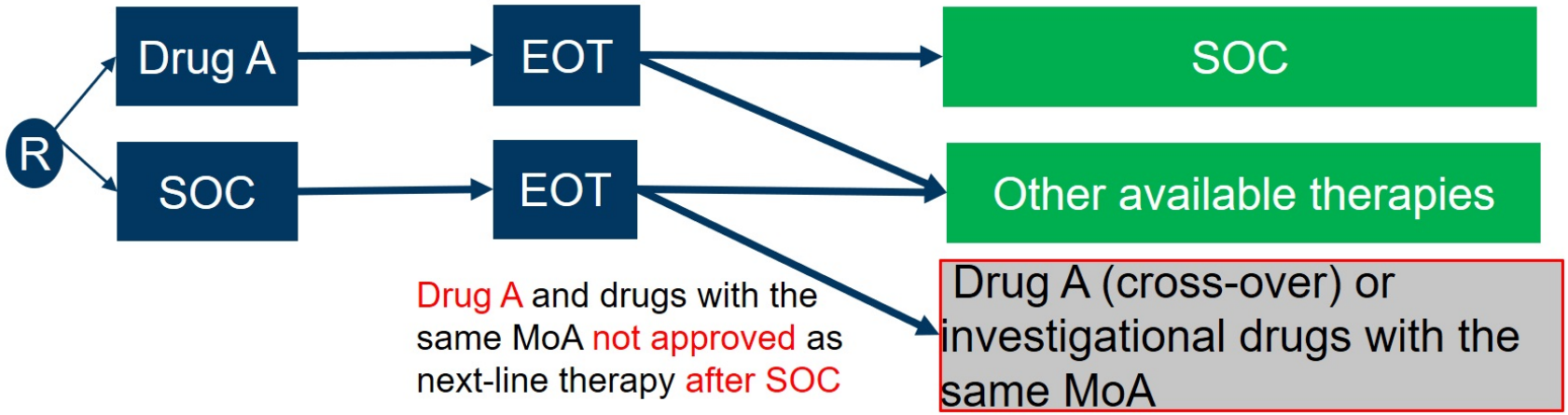

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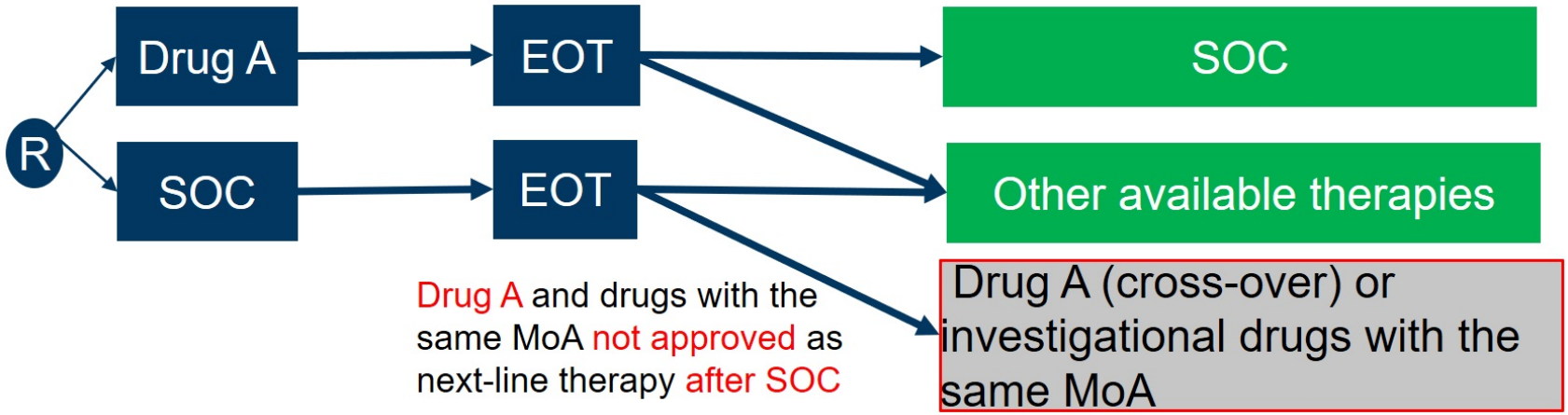

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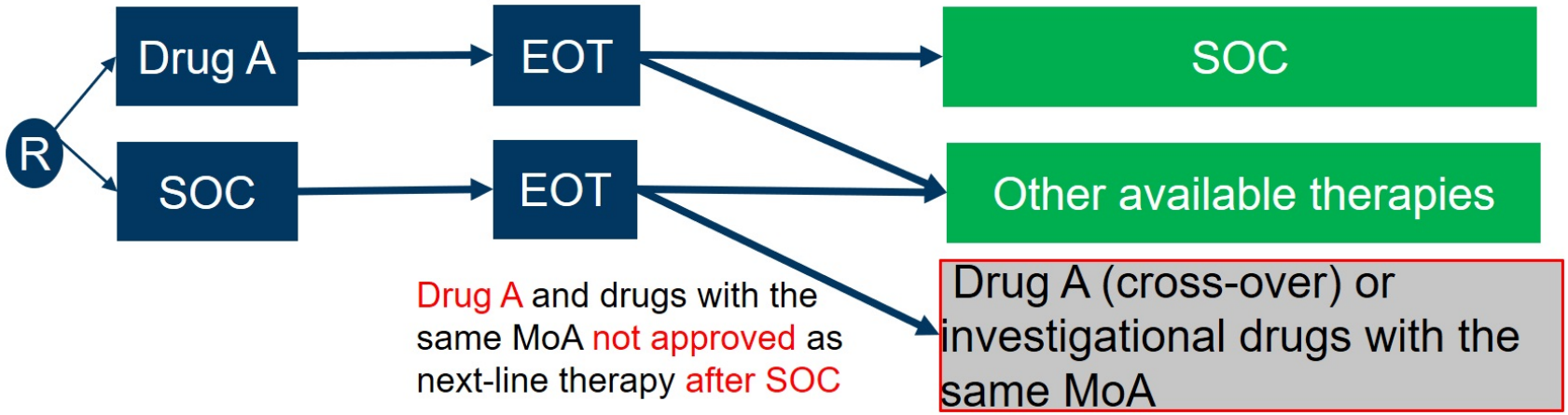

Subsequent therapy after EOT **does not** reflect clinical practice:

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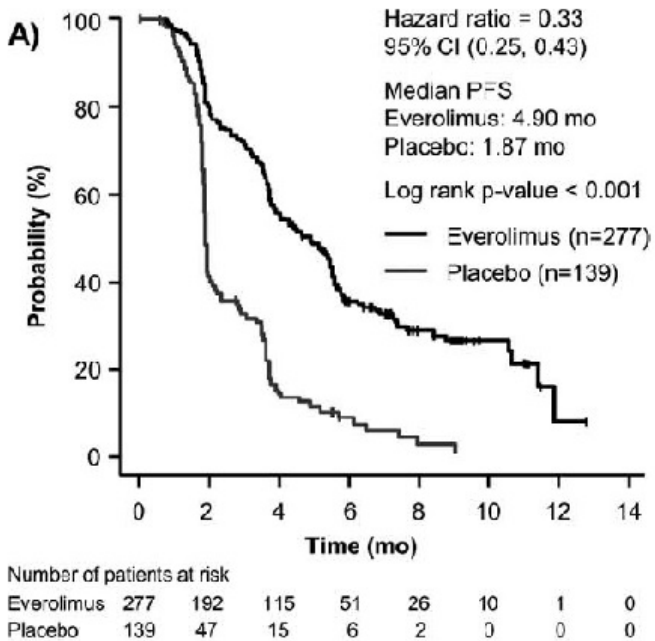
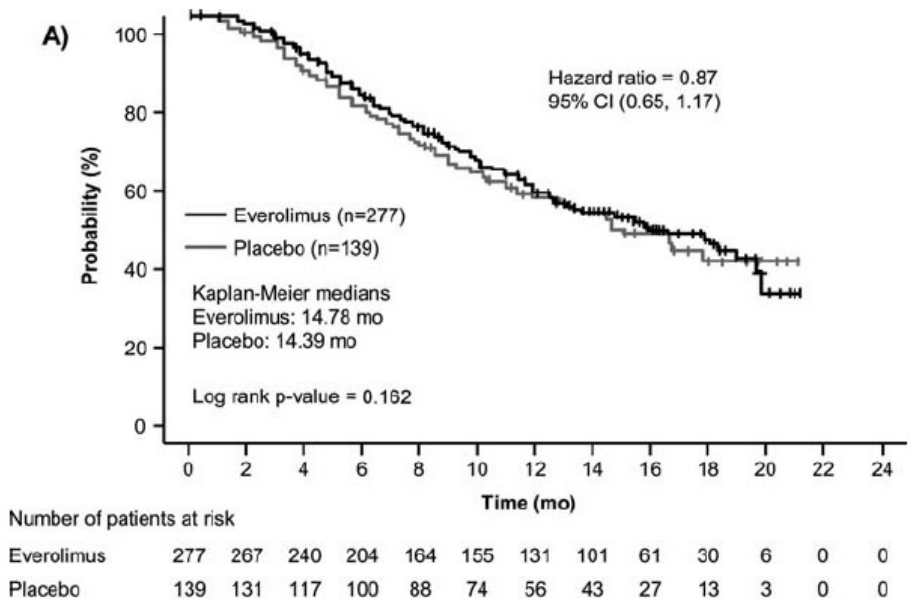
- Treatment policy estimand relevant?
- Benefit on OS without cross-over more informative? **Hypothetical estimand**!

RECORD-1





RECORD-1: Motzer et al. (2010).

Further examples: GRID, Demetri et al. (2016); GLARIUS, Herrlinger et al. (2016), Javelin Lung 200, Barlesi et al. (2019).

Randomized but not treated

- **Blinding** often infeasible.
- Checkmate-37:
  - **20% vs 1.5%**.
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Overall survival in all randomized patients interpretable?

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A statistically significant improvement in PFS was demonstrated among patients treated with STIVARGA compared to placebo (see Table 8 and Figure 2).

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Nivolumab SmPC:

There was no statistically significant difference between nivolumab and chemotherapy in the final OS analysis. The primary OS analysis was not adjusted to account for subsequent therapies, with 54 (40.6%) patients in the chemotherapy arm subsequently receiving an anti-PD1 treatment. OS may be confounded by dropout, imbalance of subsequent therapies and differences in baseline factors.

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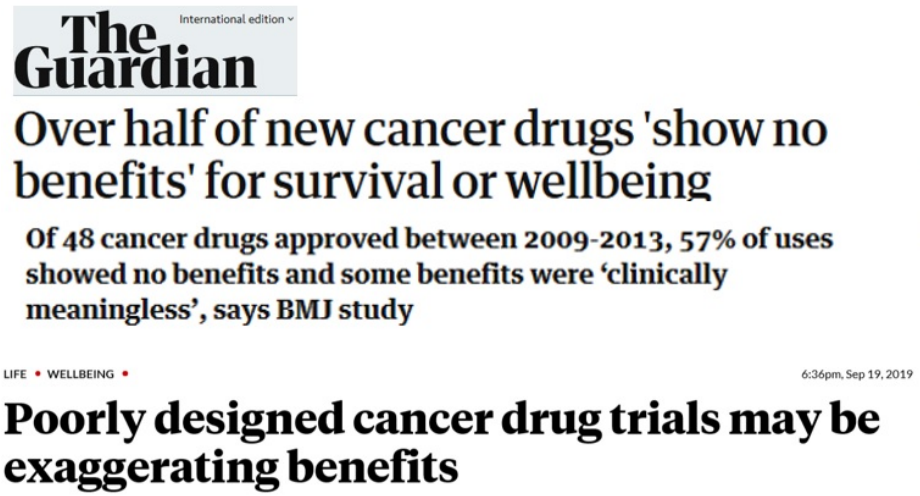

The Guardian International edition

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LIFE • WELLBEING • 6:36pm, Sep 19, 2019

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REUTERS

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PHARMALOT

STAT+

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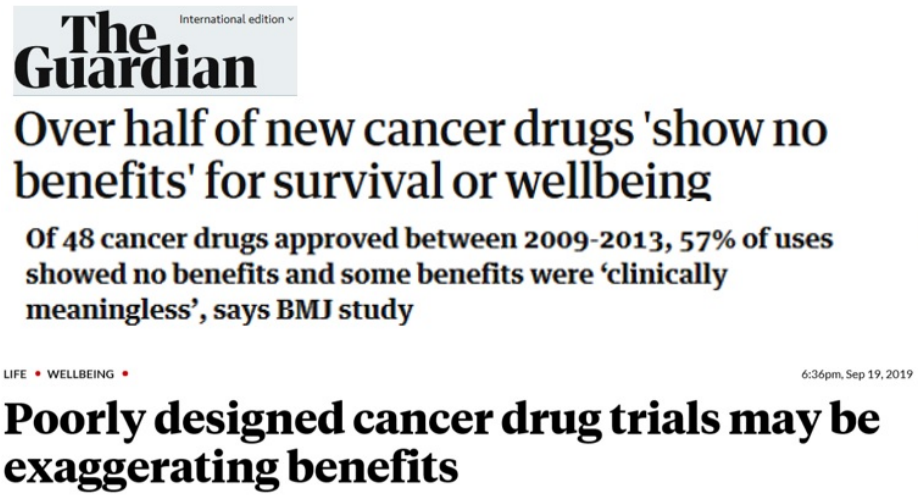
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Driven by

- non-significant result
- for treatment-policy OS estimand
- when subsequent therapies do not reflect clinical practice!

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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-

ELSEVIER

European Journal of Cancer
Volume 136, September 2020, Pages 176-185

Original Research

Progression-free survival is a suboptimal predictor for overall survival among metastatic solid tumour clinical trials

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Relevant for patients and prescribers in label: **effect of STIVARGA on OS if placebo-treated patients did not have possibility to cross-over to STIVARGA after PD?**

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$\Rightarrow$ hypothetical strategy for intercurrent event of cross-over.

Treatment switching in immuno-oncology

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Treatment policy effect for OS really what we are interested in?

How DO we estimate OS effect?

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Hypothetical estimand?

Estimands for 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 cross-over at any time*	*Evaluate OS benefit adjusted for treatment cross-over upon progression*
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 (1excluding investigational drug)	Sequence of investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapy (excluding investigational drug)
Strategy for addressing intercurrent events (IEs)	IE: Start of subsequent therapy at any time (other than cross-over)	Treatment policy	Hypothetical	Treatment policy	Treatment Policy
	IE: Cross-over to investigational drug without observed progression	Treatment policy	Hypothetical	Hypothetical	Treatment Policy
	IE: Cross-over to investigational drug upon 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 RSPFT model using adjusted survival times; bootstrapped CI; KM estimates using adjusted survival times; IPCW methods could also be used	HR from two-stage method using reconstructed survival; modified KM estimates using reconstructed survival times; IPCW and RPSFT methods could be used

Manitz et al. (2022)

Conclusions treatment switching

All stakeholders - industry, regulators, payors - have an interest in **interpretable** OS estimates.

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Enables to communicate added value of drugs better.

Agenda

Estimation of average causal effect

Why do we randomize?

Estimation of average causal effect

Key assumptions:

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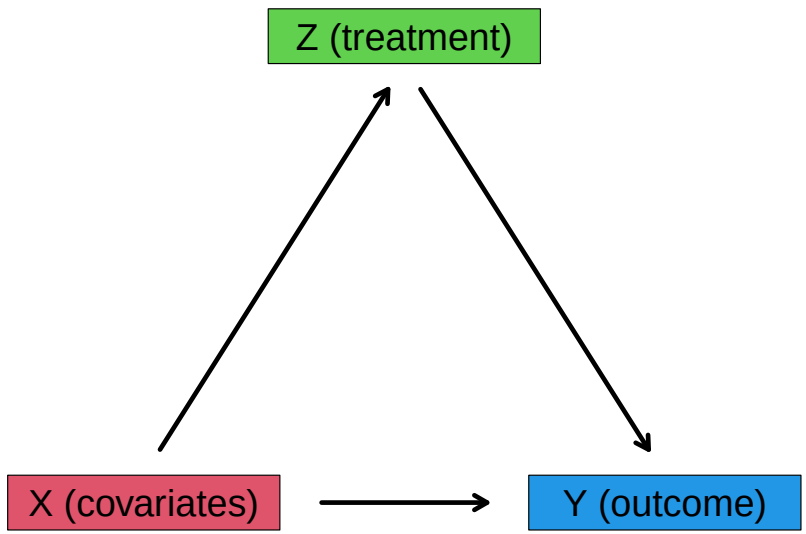

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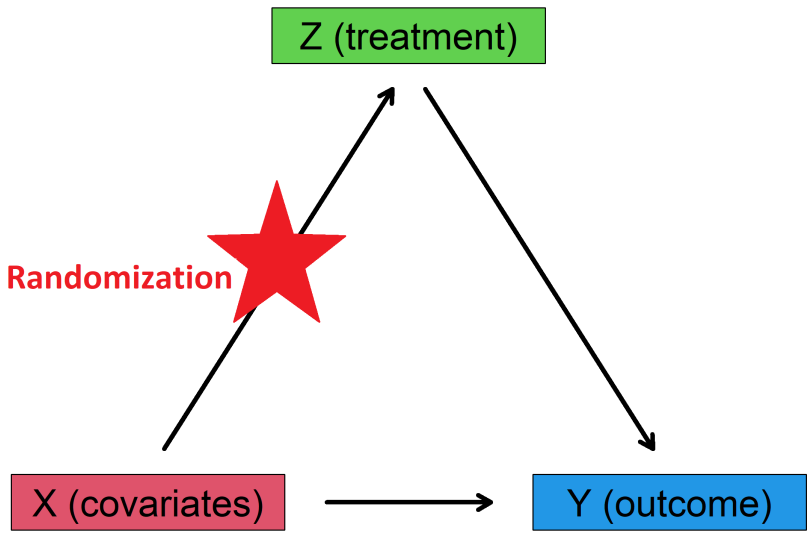

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- Randomization generates equal distributions (in both groups) of **potential outcomes**!

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Judea Pearl, American computer scientist and philosopher

Pearl (2009)

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- Patients who receive $Z = 1$ (for whom we observe $Y(1)$) might be **systematically different** from those who receive $Z = 0$ (for whom we observe $Y(0)$).

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$$
\begin{aligned}
E(Y(1) - Y(0)) &\overset{\textit{linearity of } E}{=} E(Y(1)) - E(Y(0)) \\
&\overset{\cancel{\textit{exchangeability}}}{\neq} E(Y(1)|Z = 1) - E(Y(0)|Z = 0) \\
&\overset{\textit{consistency}}{=} E(Y|Z = 1) - E(Y|Z = 0).
\end{aligned}
$$

Agenda

Subgroups by post-randomization event - principal stratification

"... The target population might be taken to be the "principal stratum" in which an **intercurrent event would occur**. Alternatively, the target population might be taken to be the principal stratum in which an intercurrent event **would not occur**. The clinical question of interest relates to the treatment effect only within the principal stratum..."

ICH (2019)

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Introductory books causal inference: Imbens and Rubin (2015), Hernán and Robins (2020).

First, let us summarize what does not work.

2-arm RCT test (T) vs. control (C)

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Do responders have higher treatment effect?

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Do responders
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"Subgroup" built by post-randomization event!

How can we make valid causal statements?

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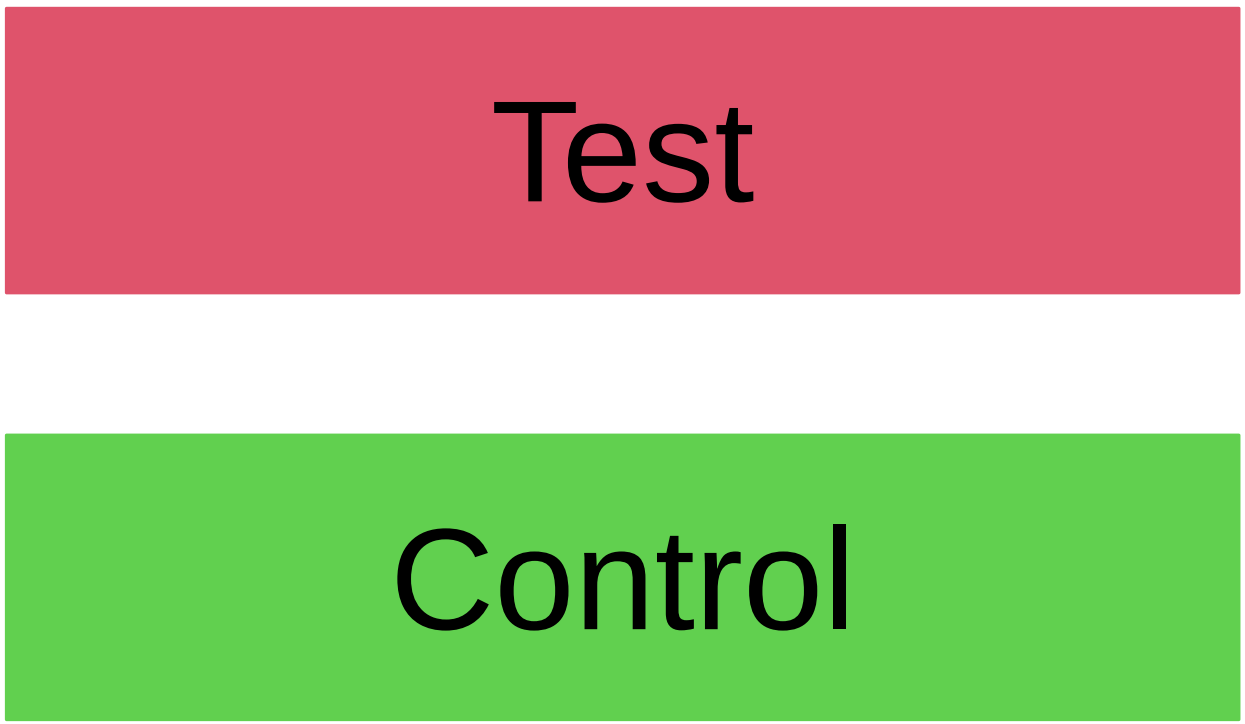
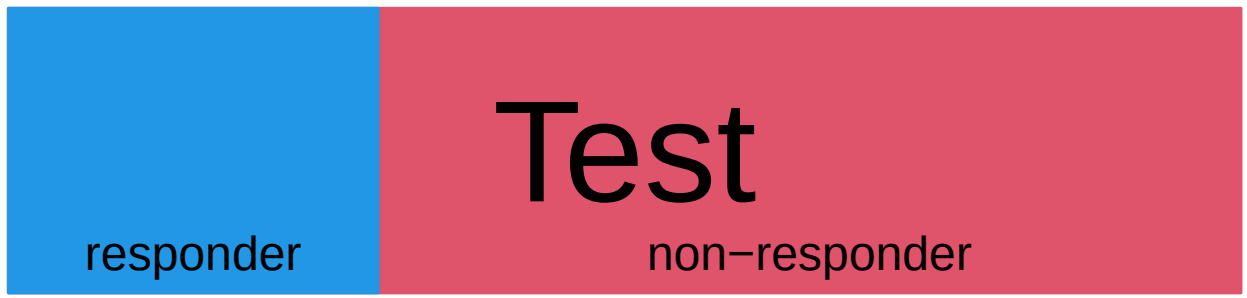
Need "matched control patients"!


Test
Control


Test
responder
non−responder



Patients who respond
if randomized to Test
had they received control

Test

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Test

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Test
responder
non−responder

For every complex problem, there is a solution that is simple, neat, and wrong.

H.L. Mencken, American Journalist

Naive analyses are misleading and do not answer causal question

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Principal stratification: "subgroup analysis for post-baseline subgroups"

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randomization + assumptions

Are such questions relevant?

Example	Scientific question	Primary endpoint	Intercurrent event	Stratum of interest
Multiple sclerosis	Treatment effect on confirmed disability progression in the subpopulation of relapse-free patients	Time to confirmed disability progression	Post-randomization relapse	Patients who would be relapse-free under both treatments
Treatment effect in early responders	Predict treatment effect on long-term primary endpoint based on early biomarker-type readout	Time-to-event	Biomarker value above or below a pre-specified threshold	Patients who would respond early under treatment vs. those that would not
Antidrug antibodies (ADA) for targeted oncology drugs	Do patients that develop ADAs on either arm still benefit from the drug?	Time-to-event	Development of antidrug antibodies because of receiving treatment	Patients who would be ADA+ under treatment
Impact of exposure on OS	Do patients with insufficient exposure have lower treatment effect?	Time-to-event	Exposure below a pre-specified threshold	Patients with low vs. non-low exposure under treatment
Prostate cancer prevention	Assess effect of treatment to prevent prostate cancer on severity of prostate cancer among those men who would be diagnosed with prostate cancer regardless of their treatment assignment	Time-to-event	Getting prostate cancer	Patients who get prostate cancer irrespective of treatment

Bornkamp et al. (2021).

OS / PFS by response.

Potential outcomes and principal stratification

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Only one observed at all $\Rightarrow$ **individual causal effect** $Y(1) - Y(0)$ not observed.

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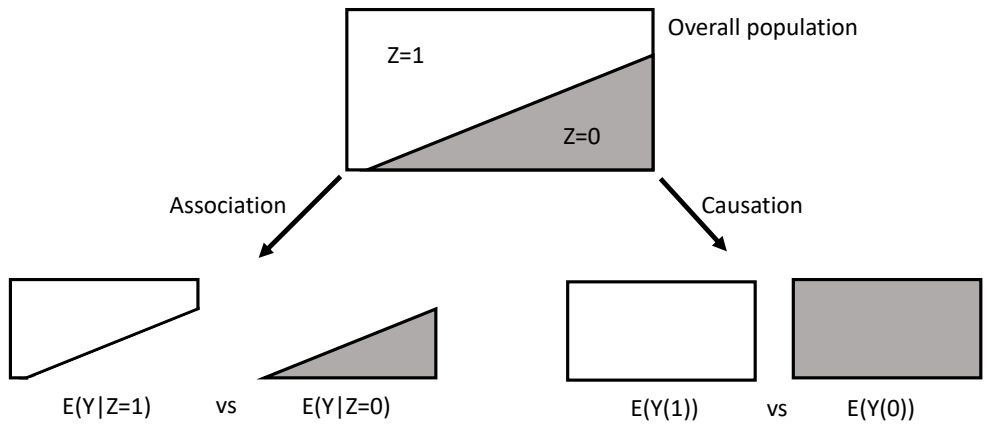

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- Estimates treatment effect in principal stratum $\{S(1) = 1\} \cap \{S(0) = 1\}$ assuming $S(1) = S(0) \Rightarrow$ response not treatment related. Assumption quite strong and **rarely justified**!

Principal stratification

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Caveat:

- For patients on test arm we observe $S(1)$, but not $S(0)$, and vice versa for patients on control arm.
- **Identification** of patients in strata of interest generally not possible, not even after observing Y and S in a given trial.

Example: antidrug antibodies in immunotherapies

- Biological drugs: may trigger immune responses $\Rightarrow$ formation of **antidrug antibodies** (ADAs).
- Scientific question: Do patients that develop ADAs still benefit from the drug?
- Y: PFS or OS.
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	ADA- under control
ADA+ under test	**Stratum of interest**
ADA- under test	

Effect measures

Primary interest:

- Compare $Y(1)$ vs. $Y(0)$ in stratum $\{S(1) = 1\}$.
- Contrast this to results in $\{S(1) = 0\}$.

Effect measure:

- (Hazard ratio **not causally interpretable**: Aalen et al. (2015).)
- Base effect measure on **survival functions**:

$$U_1(t) := P(Y(1) > t | S(1) = 1) \quad \text{and} \quad U_0(t) := P(Y(0) > t | S(1) = 1).$$

Examples:

- **Milestone** difference at $t^* > \tilde{t}$:

$$\delta(t^*) = U_1(t^*) - U_0(t^*).$$

- Time-averaged version, i.e. difference in **RMST**:

$$\int_0^{t^*} \delta(t)dt = E[\min(Y(1), t^*) - \min(Y(0), t^*)].$$

Potential outcomes, estimands, and PS

All estimand strategies can be formulated using potential outcomes:

Lipkovich et al. (2020).

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Additional complications: Y time-to-event $\Rightarrow$ outcome event = competing risk for intercurrent event. Naive analyses conditioning on observed intercurrent event:

- Compares **non-randomized** populations.
- **Immortal bias**: patients immortal until observation of S.

Liu et al. (2023).

Sensitivity analyses!

Assumptions for estimation **unverifiable**:

- "Across-world" $\Rightarrow$ even with **infinite number of observations** we could not test them.
- Only verifiable if we could observe both, patient receives control in one world and treatment in other.

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scientific knowledge + sensitivity analyses

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- Complex question $\Rightarrow$ complex analysis needed.
- Assumptions needed: scientific input + sensitivity analyses.

DOI: 10.1002/pst.2104

MAIN PAPER

Principal stratum strategy: Potential role in drug development

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Bornkamp et al. (2021)

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BBS seminar

Björn Bornkamp and Kaspar Rufibach on the Effective statistician podcast

Weighted Approach for Estimating Effects in Principal Strata With Missing Data for a Categorical Post-Baseline Variable in Randomized Controlled Trials

Shengchun Kong[a], Dominik Heinzmann[b], Sabine Lauer[c], and Tian Lu[d]

[a]Genentech, South San Francisco, CA; [b]F. Hoffmann-La Roche Ltd., Basel, Switzerland; [c]Dr. Lauer Research, Neu-Isenburg, Germany; [d]Stanford University, Palo Alto, CA

ABSTRACT

This research was motivated by studying anti-drug antibody (ADA) formation and its potential impact on long-term benefit of a biologic treatment in a randomized controlled trial, in which ADA status was not only unobserved in the control arm but also in a subset of patients from the experimental treatment arm. Recent literature considers the principal stratum estimand strategy to estimate treatment effect in groups of patients defined by an intercurrent status, that is, in groups defined by a post-randomization variable only observed in one arm and potentially associated with the outcome. However, status information might be missing even for a nonnegligible number of patients in the experimental arm. For this setting, a novel weighted principal stratum approach, namely weighted imputation regression (WRI), is presented: Data from patients with missing intercurrent event status were re-weighted based on baseline covariates and additional longitudinal information. A theoretical justification of the WRI method is provided for different types of outcomes, and assumptions allowing for causal conclusions on treatment effect are specified and investigated. Simulations demonstrated that the WRI method yielded valid inference and was robust against certain violations of assumptions. The method was shown to perform well in a clinical study with ADA status as an intercurrent event.

ARTICLE HISTORY
Received December 2020
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KEYWORDS
Anti-drug antibodies; Causal inference; ICH E9 (R1); Intercurrent event

Kong et al. (2022)

Github repository

Talk Dominik Heinzmann in BBS seminar

Agenda

Estimation of principal effects

Assumptions

Randomization not enough to estimate principal effects.

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Need assumptions.

Estimation

SUTVA:

- Underpins virtually all estimation methods.
- POs for any patient do not change with treatment assigned to other patients.
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Monotonicity:

- $S(1) \geq S(0) \Rightarrow$ patients that are ADA+ on control would also be ADA+ on test.
- Patient with $S(0) = 1$ observed $\Rightarrow$ would know that $S(1) = 1 \Rightarrow$ upper-left stratum in table empty.
- Allows estimation of principal stratum prevalences.

Estimation

Exclusion-restriction:

- Assume $Y(0) = Y(1)$ (no treatment effect) for patients $\{S(0) = 0\} \cap \{S(1) = 0\}$ and $\{S(0) = 1\} \cap \{S(1) = 1\}$.

	$S(0) = 1$	$S(0) = 0$
$S(1) = 1$	no causal effect of Z on Y	$\{S(1) = 1\} \cap \{S(0) = 0\}$
$S(1) = 0$	$\{S(1) = 0\} \cap \{S(0) = 1\}$	no causal effect of Z on Y

- Randomization Z exclusively affects outcome through intercurrent event S.
- Angrist et al. (1996), Joffe et al. (2007).

Estimation approaches: joint models

Joint models, Frangakis and Rubin (2002):

- Model for outcome given PS membership: $Y(0), Y(1)|S(1), S(0)$.
- Model for PS membership $S(0), S(1)$.
- Multiply likelihoods $\Rightarrow$ joint model for Y and S.
- **Treat unobserved potential outcomes as missing data** $\Rightarrow$ integrate out to define likelihood.
- Can easily include covariates in either model.
- Use (weakly informative) priors to govern "strength" of assumption, e.g. monotonicity.
- Application: Magnusson et al. (2019), Public Assessment Report of the European Medicines Agency (EPAR):
  European Medicines Agency, Committee for Medicinal Products for Human Use (2019).

Estimation approaches: principal ignorability

Principal ignorability (PI, or conditional independence):

- Approach very similar to propensity scoring in observational studies.
- Specify **separate models** for Y and S.
- Conditional on baseline covariates X: $Y(0)$ and $S(1)$ independent.
- X: all variables that **confound** $Y(0)$ and $S(1)$ $\Rightarrow$ once X are known, $S(1)$ provides no further information on $Y(0)$ (+ vice versa):

$$p(Y(0)|X, S(1)) \quad = \quad p(Y(0)|X).$$

- Allows modeling of $Y(0)$ and $S(1)$ **just based on** X. Unobserved outcome not needed in model.
- Assumption is **across worlds**.

Estimation approaches: principal ignorability

Estimand of interest:

$$P(Y(1) > t | S(1) = 1) - P(Y(0) > t | S(1) = 1).$$

Estimation:

- $P(Y(1) > t | S(1) = 1)$: survival function in ADA+ in treatment arm.
- $P(Y(0) > t | S(1) = 1)$: tricky, because $Y(0)$ and $S(1)$ **never jointly observed**.
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Randomization is key:

- Ensures that relationship $X - S$ same in both groups.
- Allows prediction of PS membership in control group using model from treatment group.

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  - **Matching**.
- See propensity score literature for assessment of methods, e.g. Austin (2011).

Estimation under principal ignorability for ADA example

Choice of X:

- Adjust for all confounders that make $Y(1)$ and $S(0)$ (+ vice versa) independent.
- Only adjust for X that confound Y and S across worlds: predictors of S and Y. Similar to observational studies: $X =$ predictors of treatment and outcome.
- **Do not include** covariates that "only" help predict S but have no impact on Y.
- Similar to considerations for observational studies.

Agenda

Impact of ICH E9(R1) and conclusions

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- **Shift of resources** from analysis / filing to design.
- Alternative approaches to avoid non-informative treatment policy estimand if its assumption very likely to be violated.

Agenda

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- ICH E9 addendum, accompanying training material.

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- Industry association special interest groups: `www.oncoestimand.org`, Estimands in neuroscience, Estimands implementation working group.

A problem well put is half solved.

John Dewey
American Philosopher and Educator

Design trumps analysis.

Don Rubin, American Statistician

Rubin (2008)

Thank you for your attention.

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Doing now what patients need next

R version and packages used to generate these slides:

R version: R version 4.2.2 (2022-10-31 ucrt)

Base packages: stats / graphics / grDevices / utils / datasets / methods / base

Other packages: ComparisonSurv / survival / prodlim

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