Answering Old Questions with New Tools: Application of the ICH E9 Addendum in Oncology

Kaspar Rufibach
Methods, Collaboration, and Outreach Group, F. Hoffmann-La Roche, Basel
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Acknowledgments

This material:

- was first presented at the 76th Deming Conference on Applied Statistics on 9th December 2020 link,
- by Kaspar Rufibach and **Evgeny Degtyarev (Novartis)**.
- Sections on CAR-T and switching had initially been prepared by Evgeny.

Acknowledgments

We borrowed from slides by

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

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

Keaven Anderson (Merck) and **Frank Bretz** (Novartis).

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

The intellectual illness of clinical drug evaluation that I have discussed here can be cured, and it will be cured when we restore intellectual primacy to the questions we ask, not the methods by which we answer them.

Lew Sheiner
American Clinical Pharmacologist

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Sheiner (1991)

After emailing scientific question back three times:

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So hard exercise, it made me realise I am not sure what exactly we want.

After emailing scientific question
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Roche quantitative scientist

Agenda

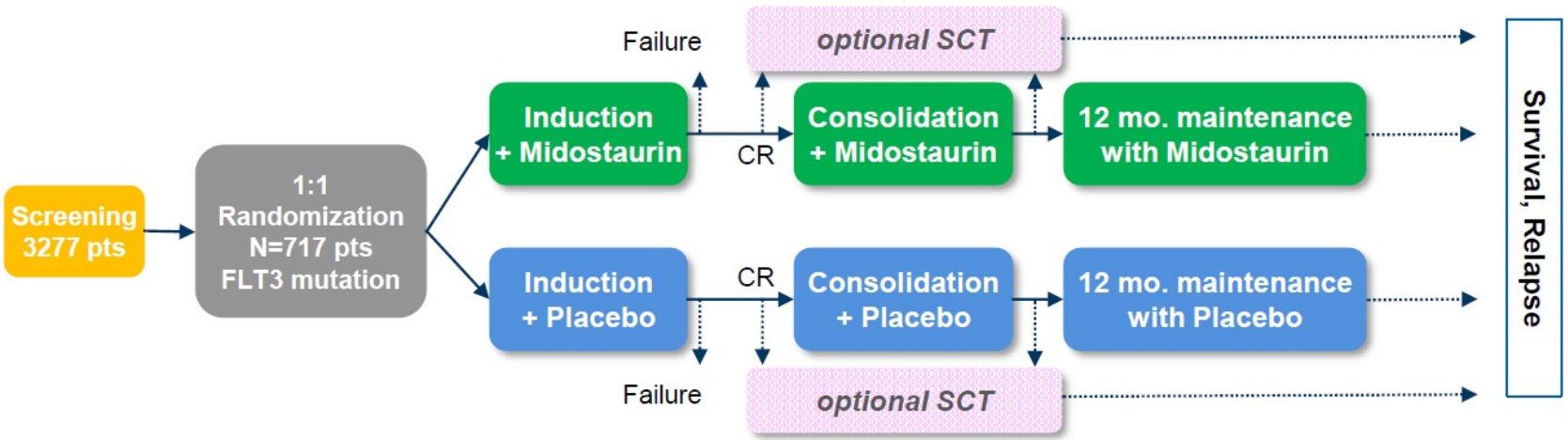
1. Case study: hematology
2. Case study: treatment switching
3. Impact and conclusions
4. Backup: ICH E9(R1) addendum: Why? And what's new?
5. Backup: Industry working group *Estimands in oncology*
6. Backup: Subgroups by post-randomization event - principal stratification
7. Backup: Estimation of average causal effect
8. Backup: Estimation of principal effects

Agenda

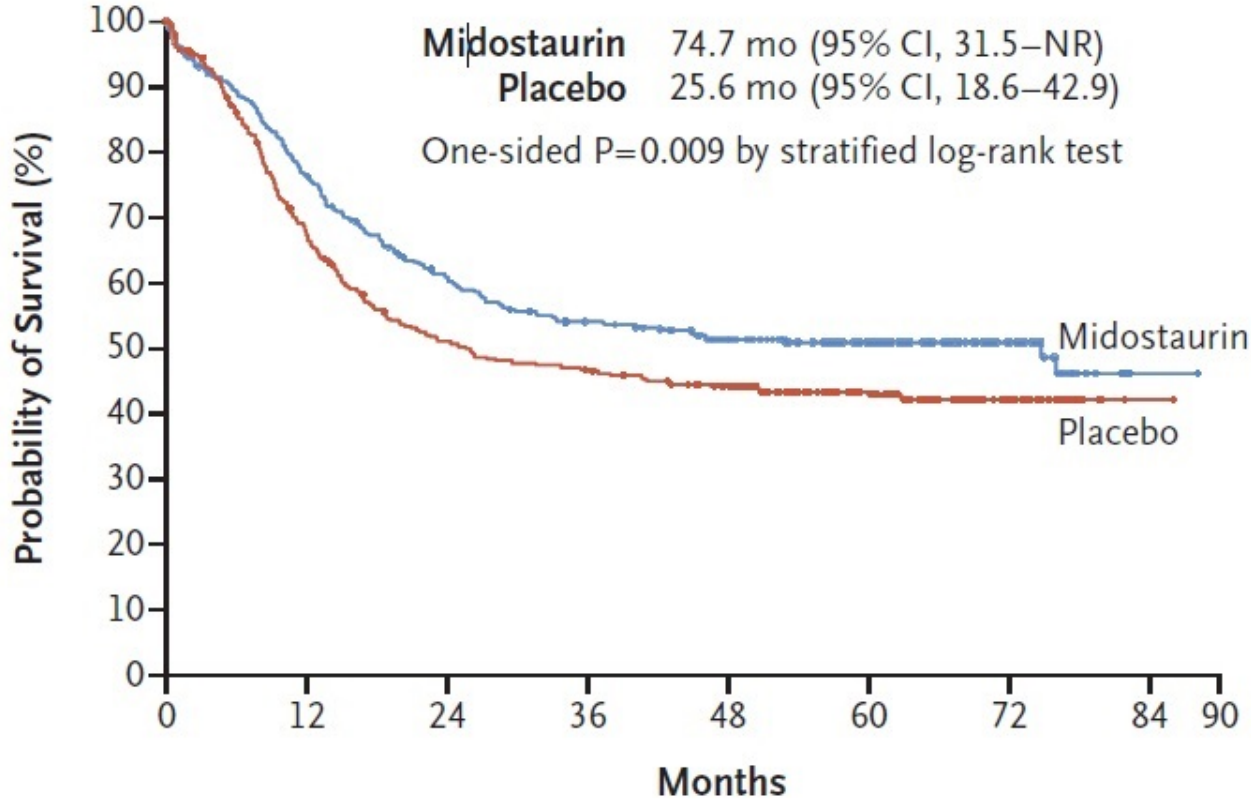
Case study: hematology

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**.

AML:

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  - Component of treatment strategy with potential major impact on B/R.

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- SCT:
  - Component of treatment strategy with potential major impact on B/R.
  - Impact not clearly outlined in trial objective.
- Maintenance: Despite explicit inclusion in trial objective $\Rightarrow$ **inconsistently included in approved labels EMA and FDA**.

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- Control: Daunorubicin-AraC induction + placebo, AraC + placebo consolidation in pts with a CR, option to receive SCT in CR.

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Summary measure: hazard ratio.

Complex (multiphase) strategies:

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Non-proportional hazards?

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Cure?

What do these findings have in common?

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They can all be anticipated!

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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

Case study: treatment switching

Good old days: Herceptin

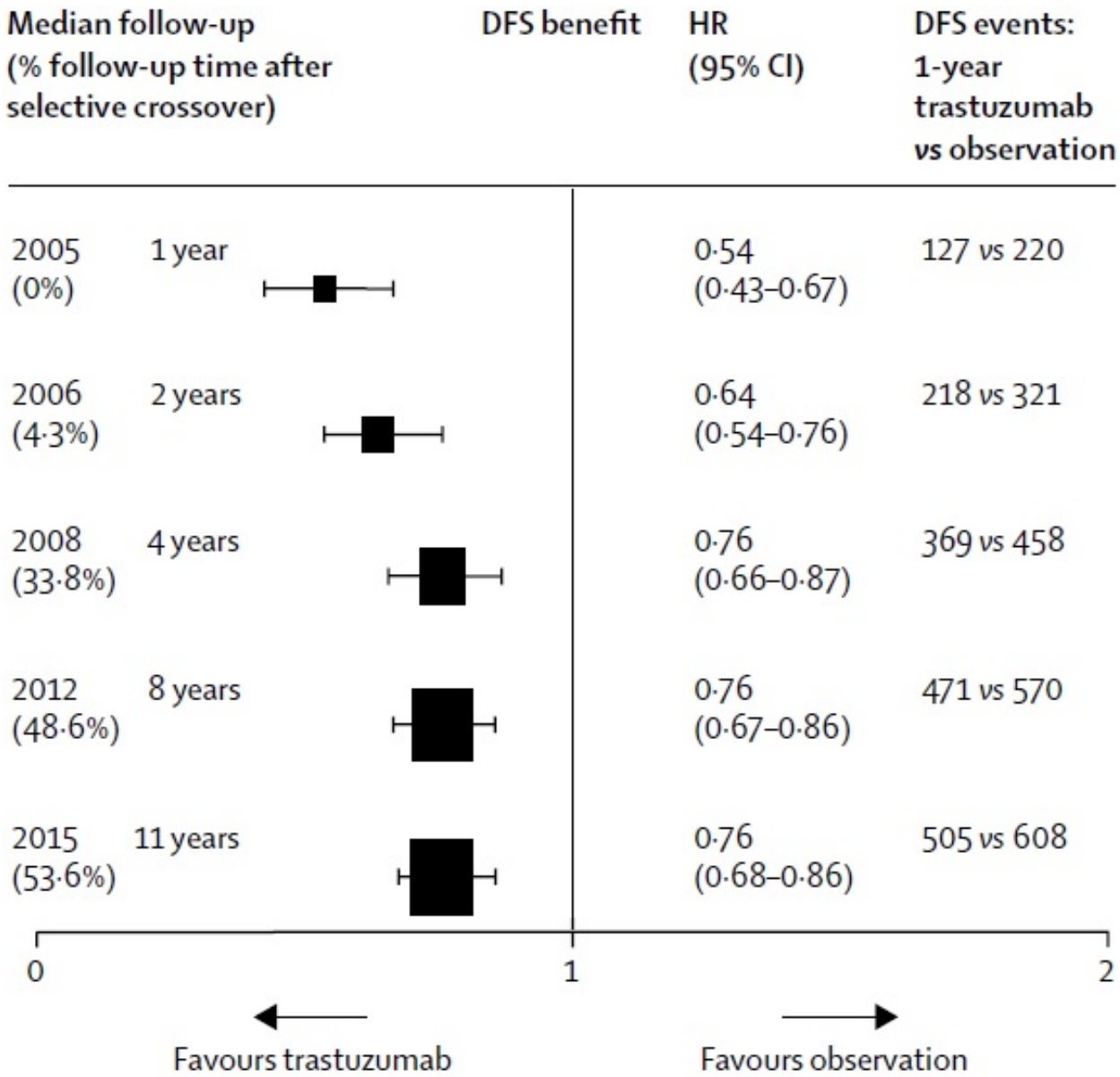
HERA

- **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**.

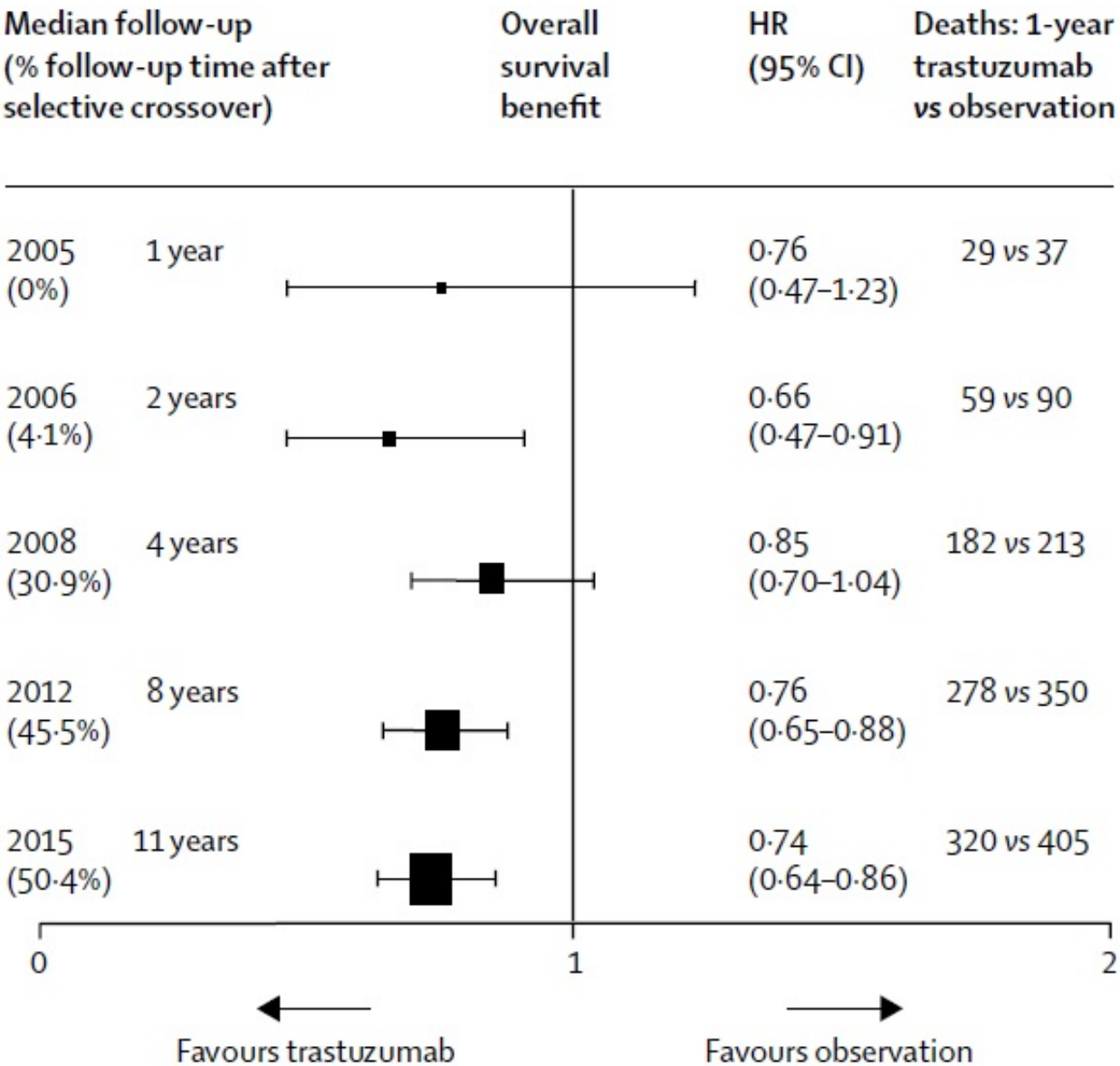
Piccart-Gebhart and Procter (2005):

- 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



HERA: comments

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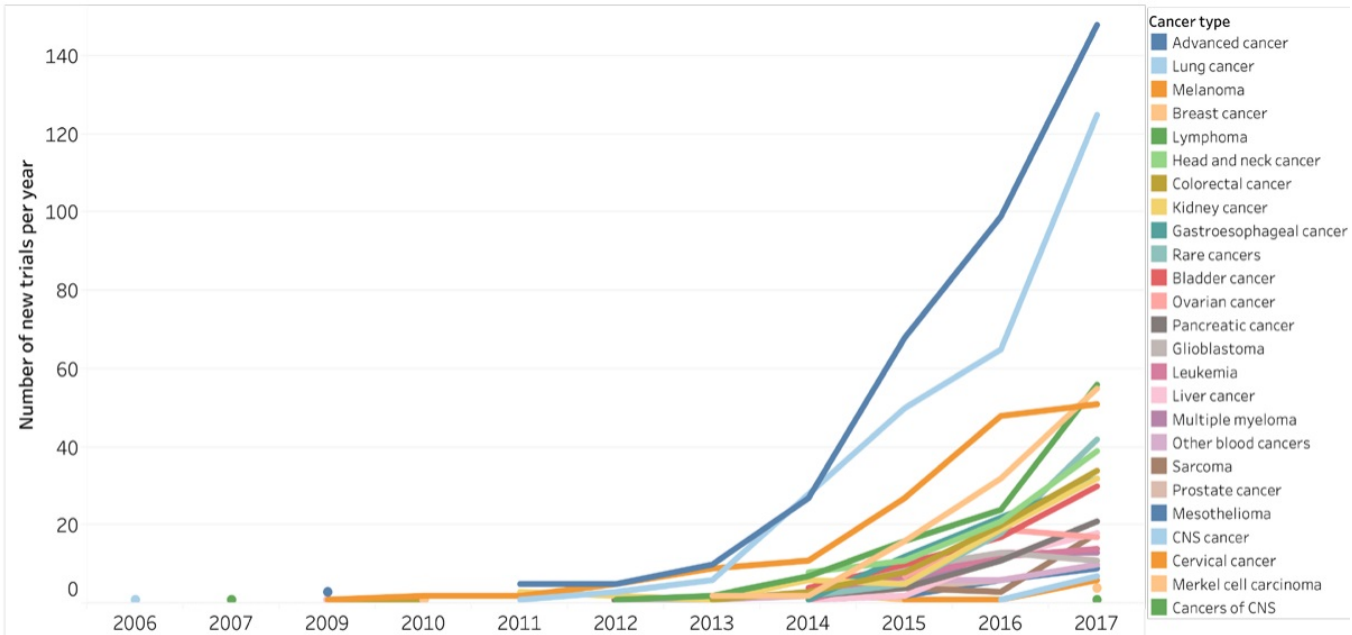
Treatment policy estimand interpretable.

Oncology landscape has changed!

Clinical trials with anti-PD1/PDL1 agents

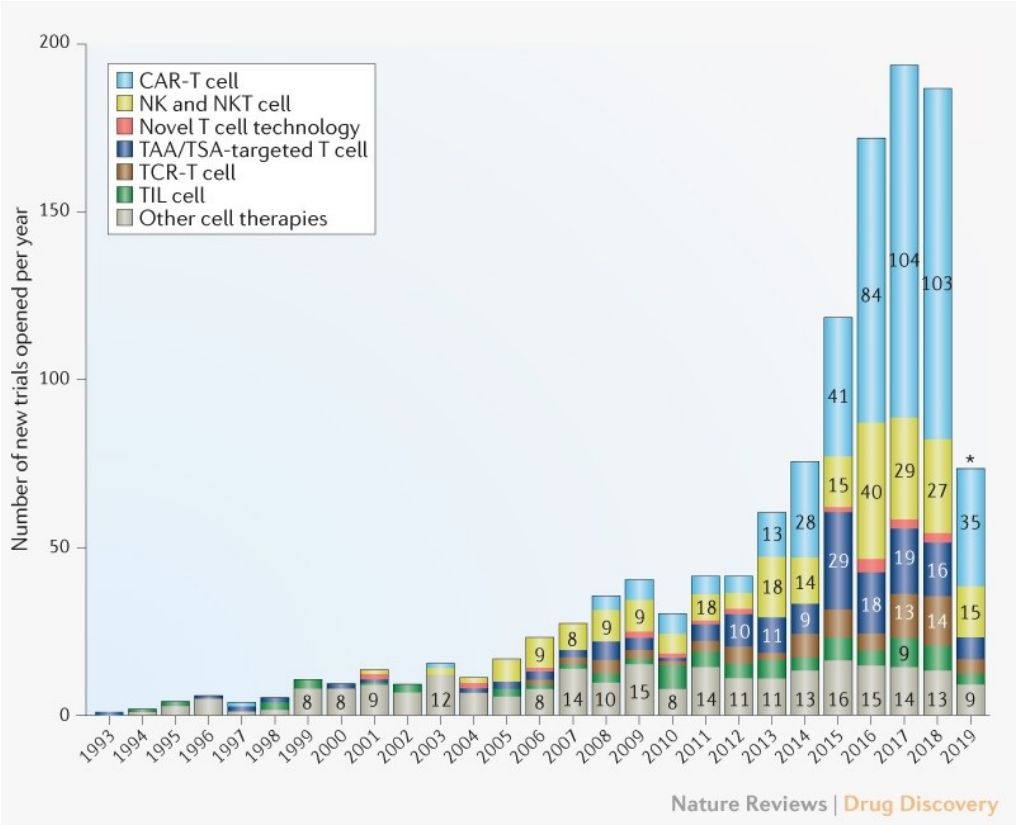


1 in 2006, **1502** in Sep 2017, **2250** in Sep 2018, **2975** in Sep 2019.

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!

- durable responses,
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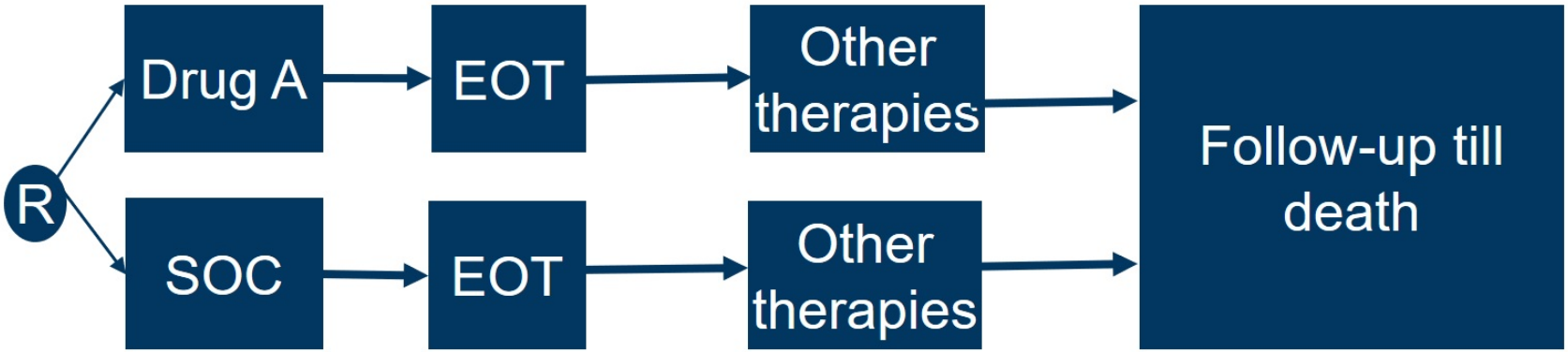
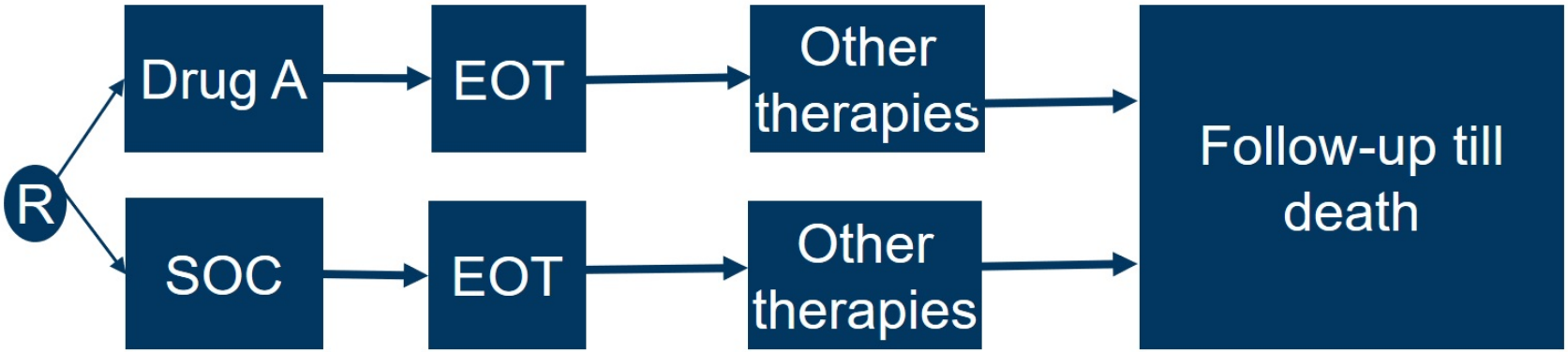
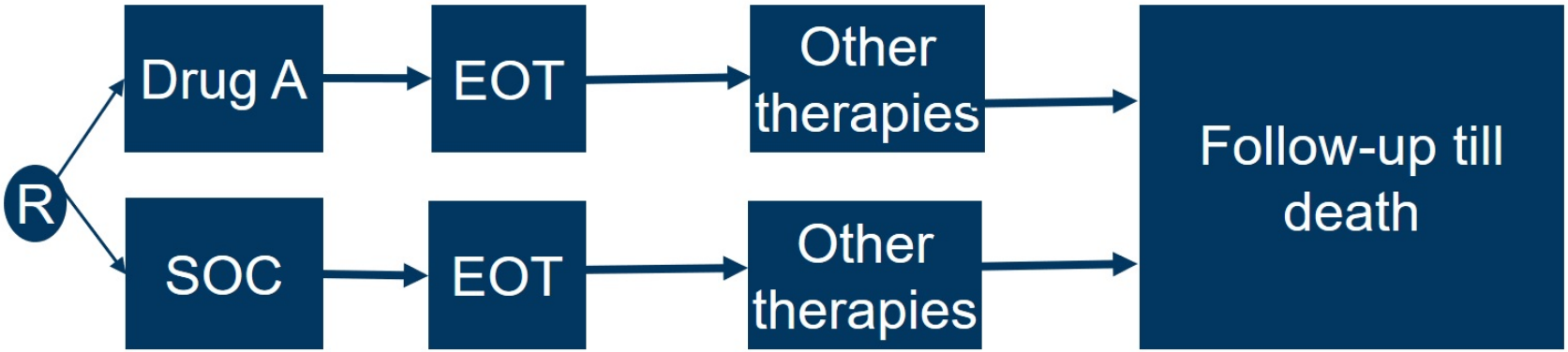
But what does it mean for clinical trials?


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



Typical OS definition:



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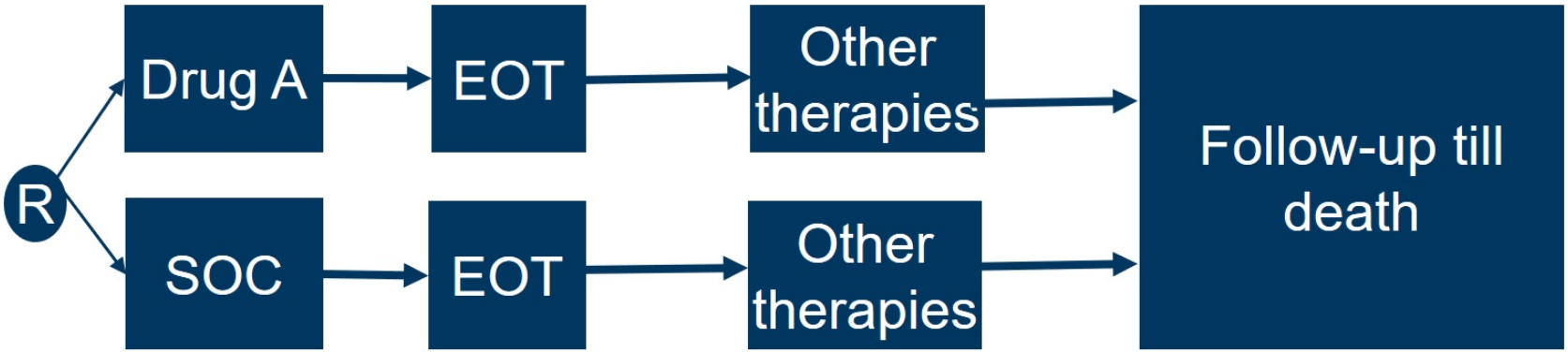

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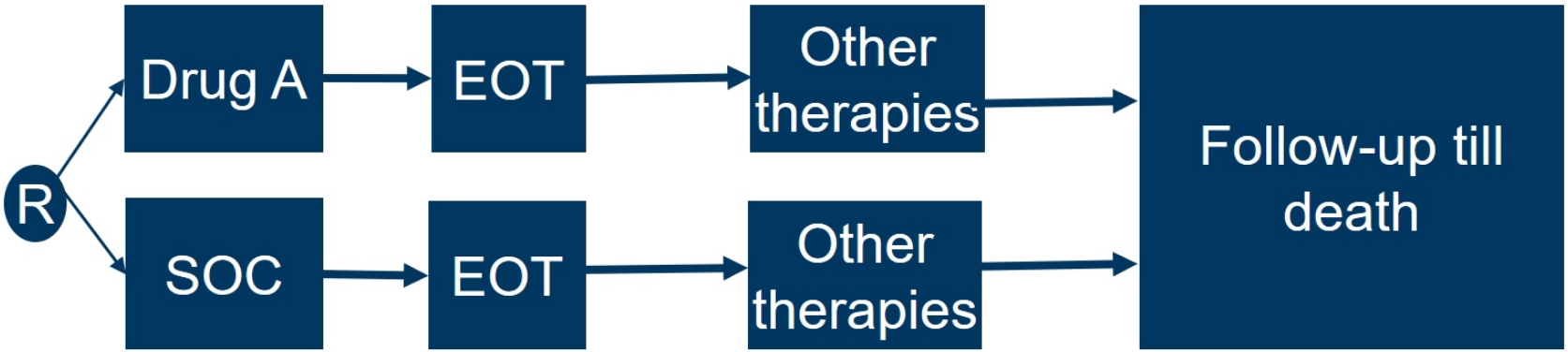

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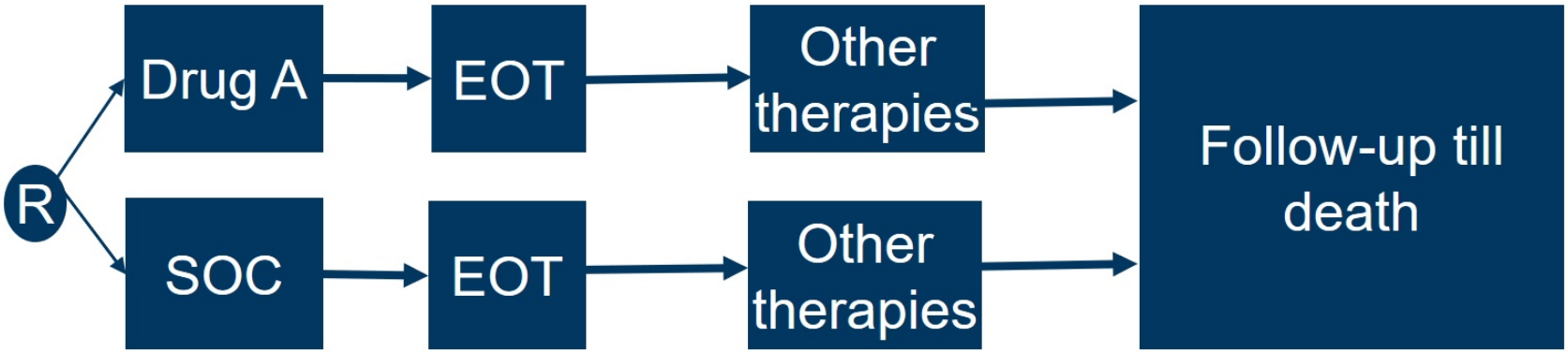

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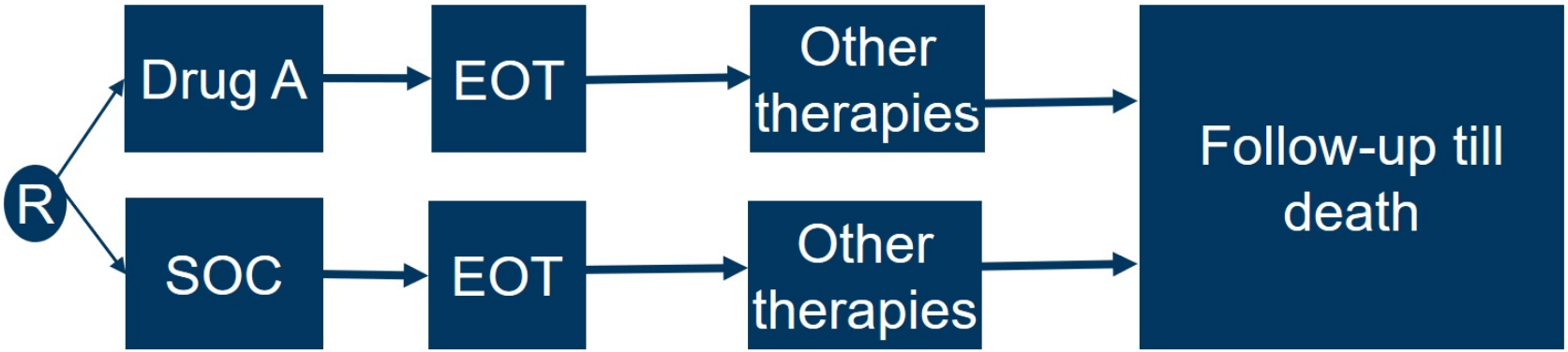

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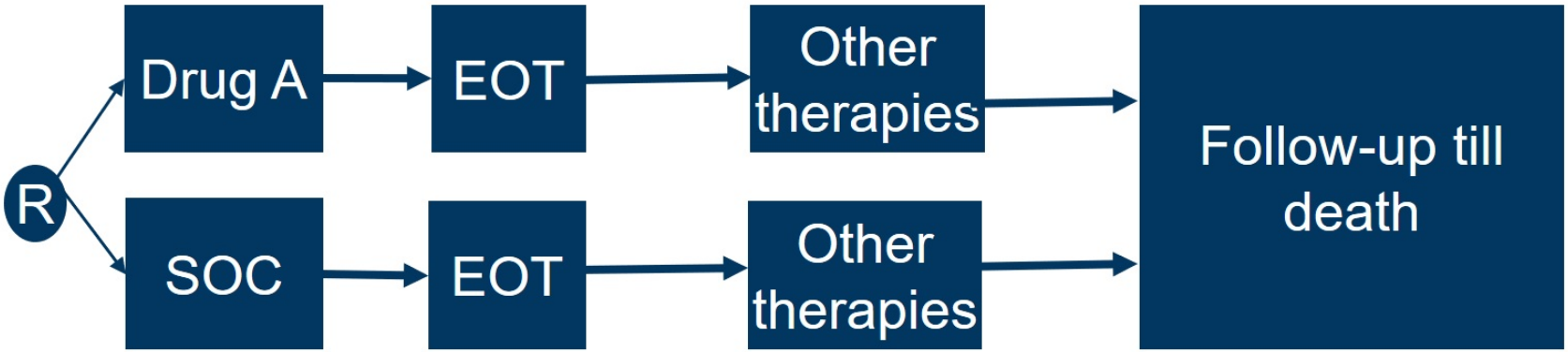

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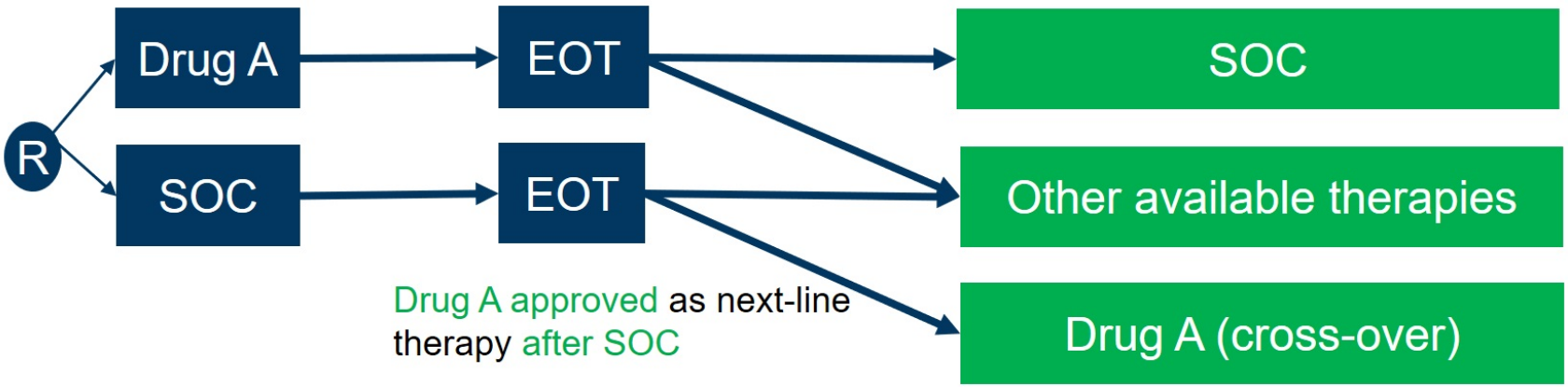
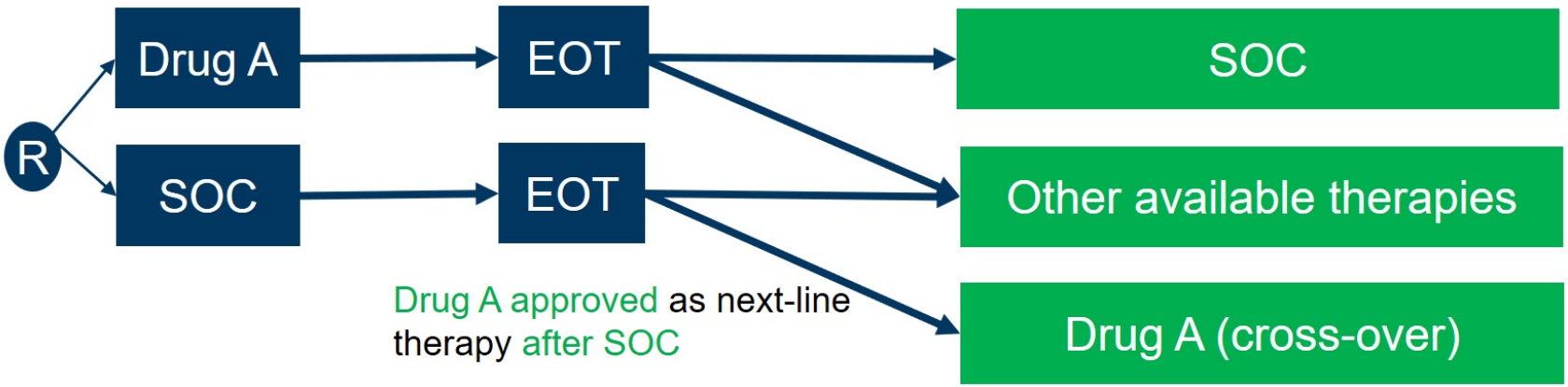
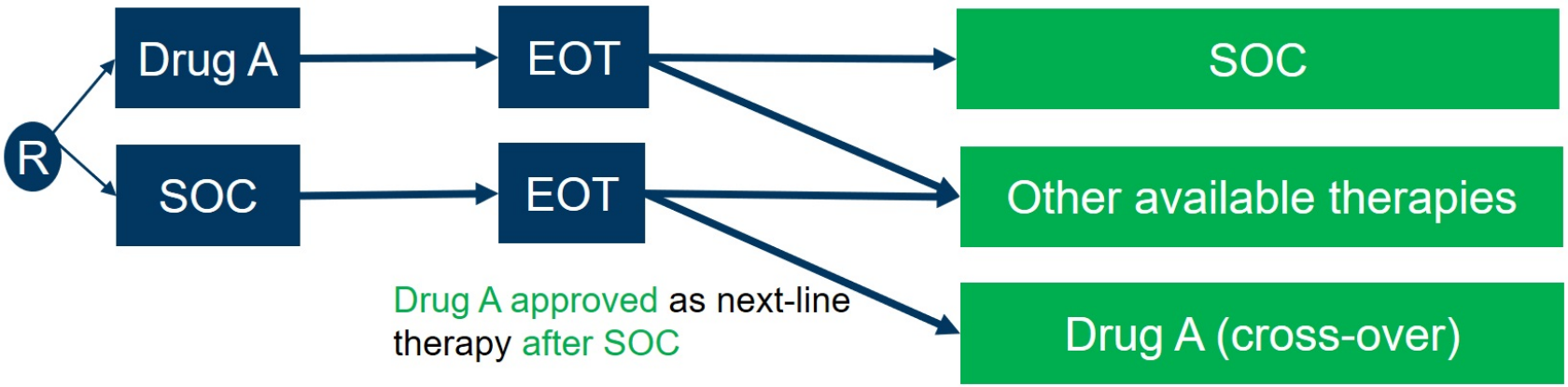
Treatment policy OS estimand **interpretable** if subsequent therapy after EOT reflects **clinical practice**.


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



Subsequent therapy after EOT reflects clinical practice.



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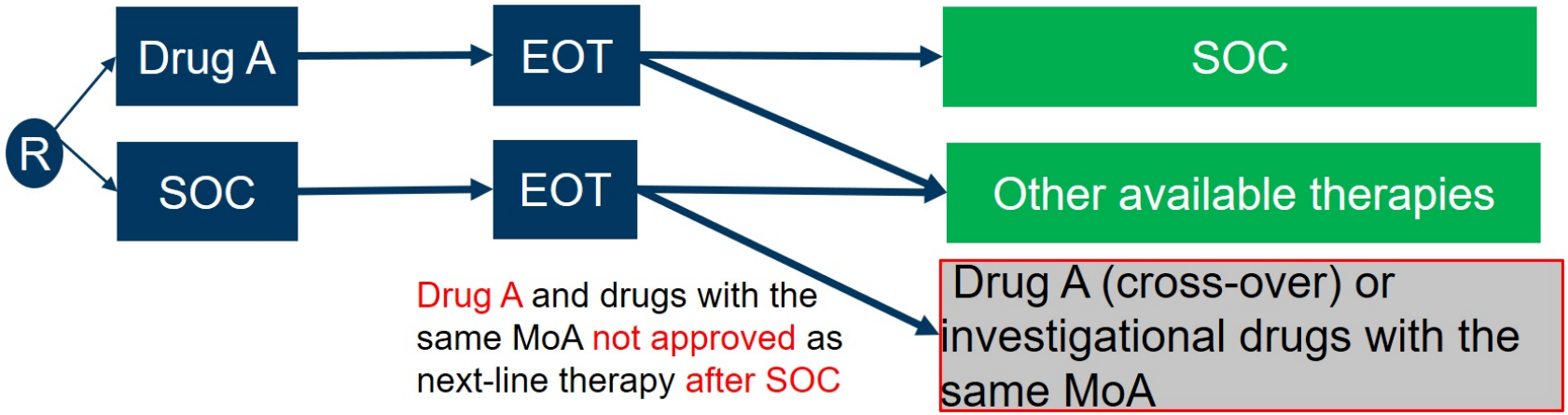
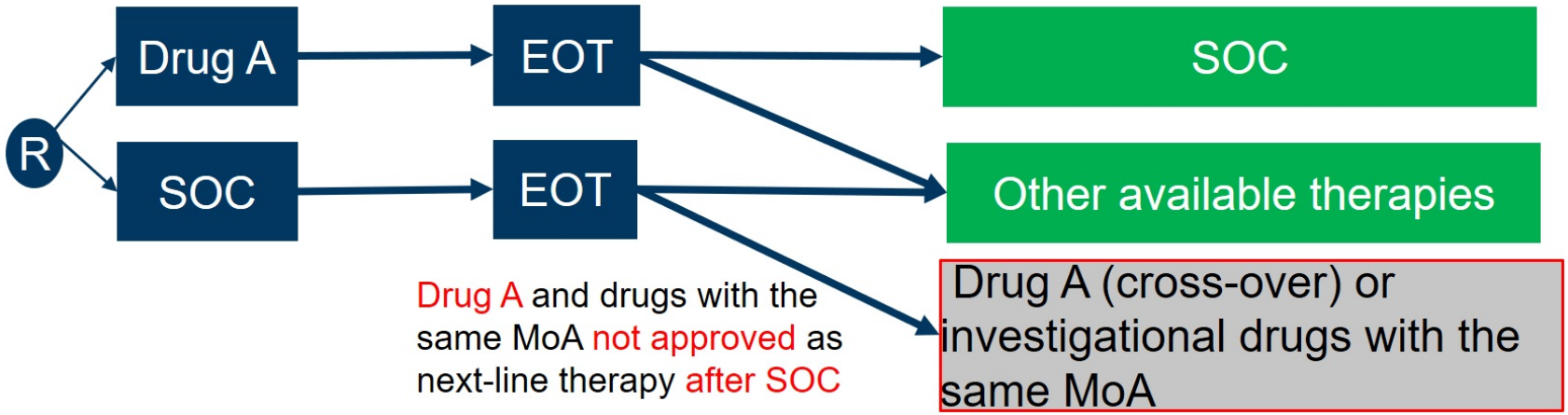

R
Drug A
SOC
EOT
EOT
SOC
Other available therapies
Drug A (cross-over) or investigational drugs with the same MoA
Drug A and drugs with the same MoA not approved as next-line therapy after SOC



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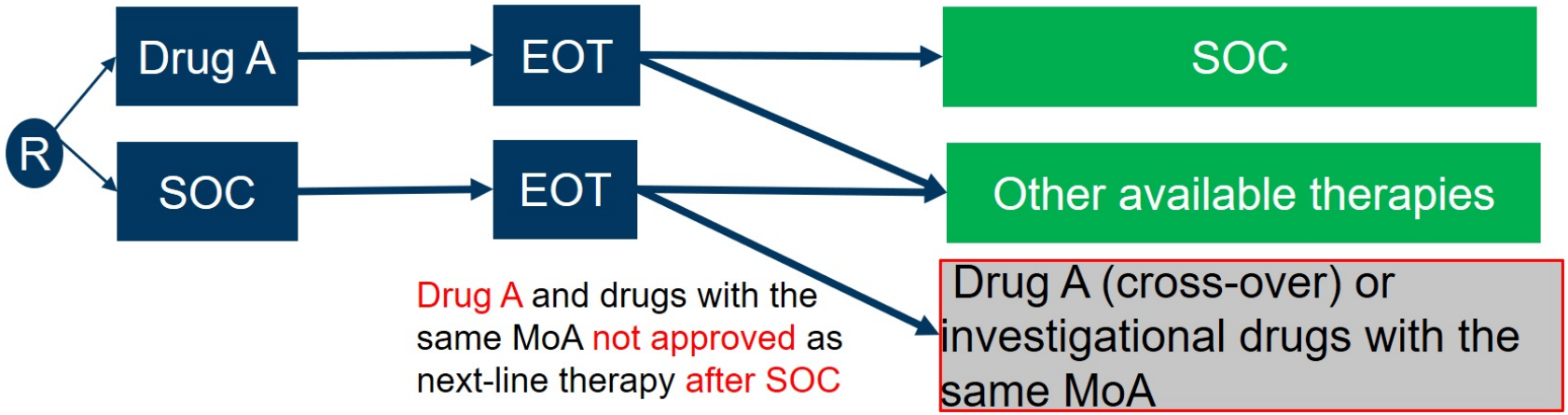

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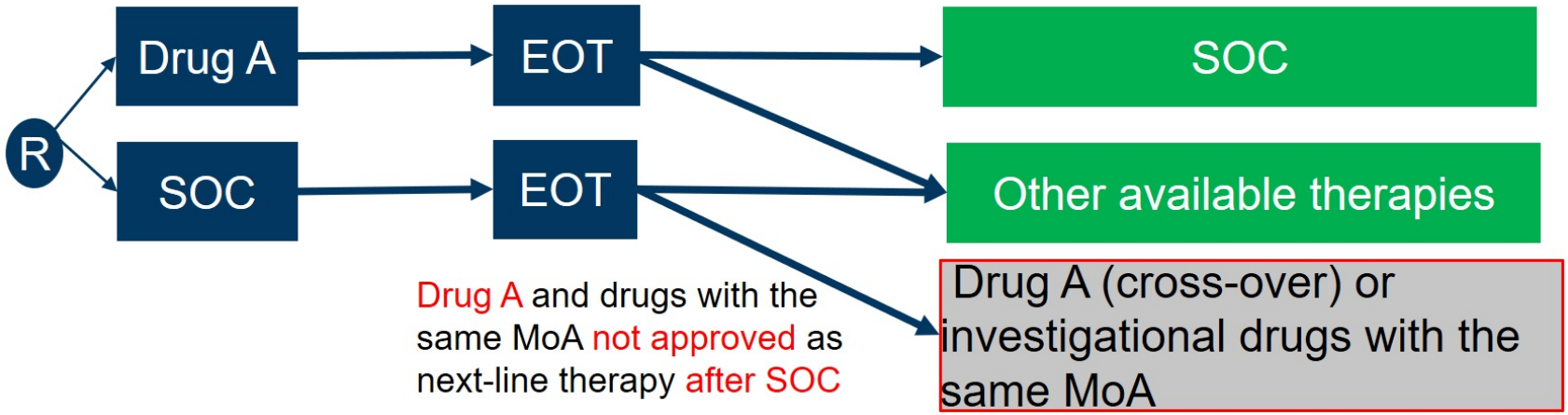

Subsequent therapy after EOT **does not** reflect clinical practice:

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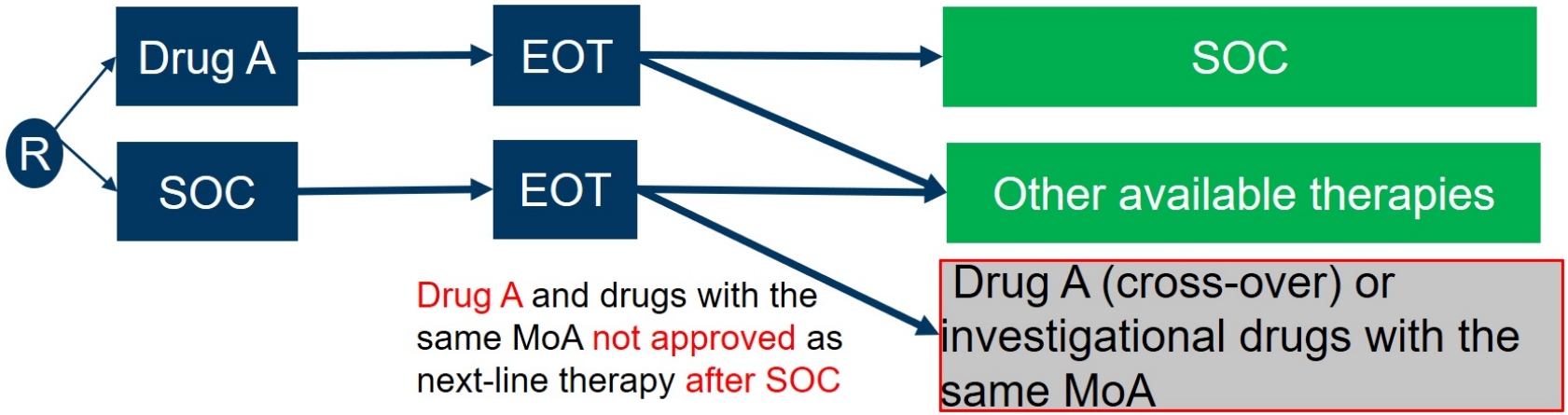
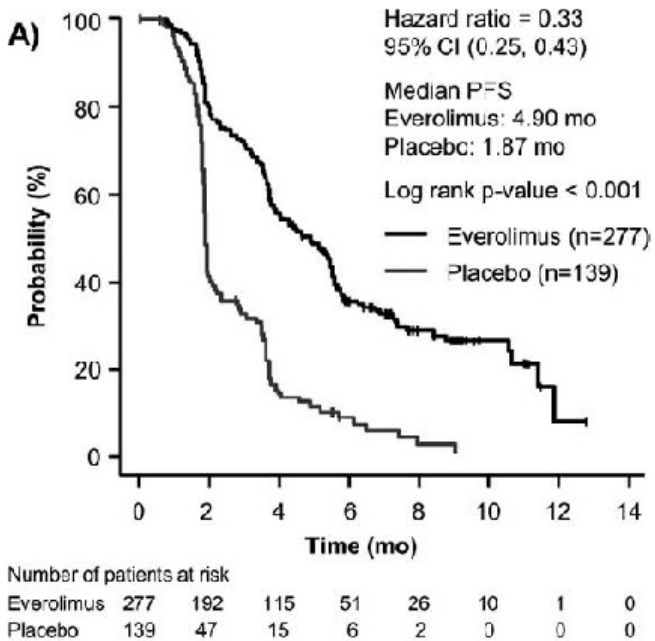
- Treatment policy estimand relevant?

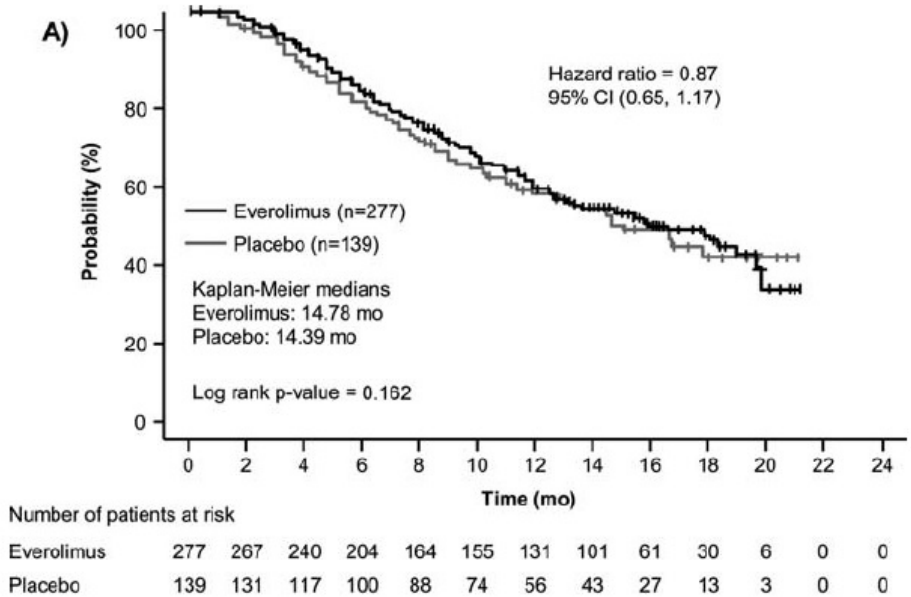


Subsequent therapy after EOT **does not** reflect clinical practice:

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

RECORD-1





RECORD-1: Motzer *et al.* (2010). PFS (left) and OS (right).

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%**.
  - Weber *et al.* (2015).
- Quantum-R:
  - **23% vs 1.6%**.
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Overall survival in all randomized patients interpretable?

If subsequent therapies do not reflect clinical practice...

...OS description in labels is ambiguous:

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...OS description in labels is ambiguous:

Regorafenib USPI:

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

There was no statistically significant difference in overall survival at the final OS analysis, conducted at 162 OS events (Table 8). Cross-over to open label STIVARGA occurred in 58 (88%) placebo-treated patients after disease progression.

If subsequent therapies do not reflect clinical practice...

...OS description in labels is ambiguous:

Regorafenib USPI:

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

There was no statistically significant difference in overall survival at the final OS analysis, conducted at 162 OS events (Table 8). Cross-over to open label STIVARGA occurred in 58 (88%) placebo-treated patients after disease progression.

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.

If subsequent therapies do not reflect clinical practice...

...drugs are perceived as not improving survival.

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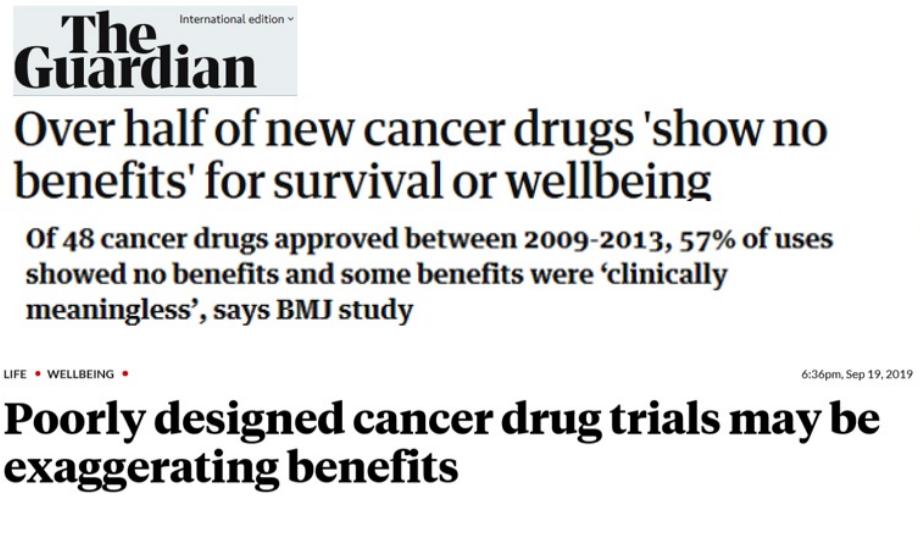
...drugs are perceived as not improving survival.



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

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

Poorly designed cancer drug trials may be exaggerating benefits

HEALTH NEWS OCTOBER 13, 2017 / 8:44 PM / 7 MONTHS AGO REUTERS

Little evidence new cancer drugs improve survival

PHARMALOT STAT+

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

By ED SILVERMAN @Pharmalot / SEPTEMBER 18, 2019

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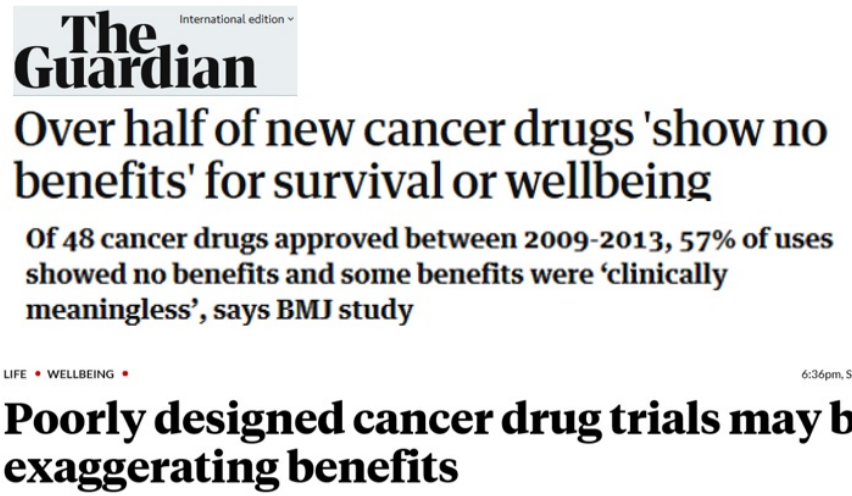

Driven by

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

If subsequent therapies do not reflect clinical practice...

...regulatory standards are perceived to be low.

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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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...hypothetical estimand represents key question of interest.

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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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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?**

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

Treatment switching in immuno-oncology

Treatment switching in immuno-oncology:

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- Availability of **non-approved** drugs (in other clinical trials) after SOC.

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- Open-label trials: Patients switch directly after randomization.
- Additional challenge: **Varying access** to such treatment across countries.

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

How DO we estimate OS effect?

How DO we estimate OS effect?

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.* (2021)

DOI: 10.1002/pst.2158

MAIN PAPER

Estimands for overall survival in clinical trials with treatment switching in oncology

Juliane Manitz[1] | Natalia Kan-Dobrosky[2] | Hannes Buchner[3] | Marie-Laure Casadebaig[4] | Evgeny Degtyarev[5] | Jyotirmoy Dey[6] | Vincent Haddad[7] | Fei Jie[8] | Emily Martin[1] | Mindy Mo[9] | Kaspar Rufibach[10] | Yue Shentu[11] | Viktoriya Stalbovskaya[12] | Rui (Sammi) Tang[13] | Godwin Yung[14] | Jiangxiu Zhou[15]

Manitz *et al.* (2021)

Conclusions treatment switching

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

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- learn together,
- understand primary and sensitivity analyses.

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Methodology may not yet be perfect: all stakeholders need to

- learn together,
- understand primary and sensitivity analyses.

Enables to communicate added value of drugs better.

Agenda

Impact and conclusions

Impact on data collection and trial planning

- Estimand **dictates data that need to be collected**.
- Each trial likely to have **multiple estimands** $\Rightarrow$ different estimands might require different data!
- Requires **multi-disciplinary** involvement from **earliest stages** of clinical trial development.
- Impacts **design of eCRF** or other data collection tools and monitoring strategy.
- Likely increased effort in recording reasons underlying **treatment or study withdrawals, or missing data**.
- Might need to reflect estimand assumptions in **sample size computation**!

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Novo Nordisk:

- Focussing on retention, keeping subjects in trial even after discontinuing trial drug.
- Increased completion rates from **90% to 98%** in type 1 diabetes and from **70% to over 90%** in obesity trials.
- Source: `https://www.dsbs.dk/moder/Estimands/HLynggaard.pdf`.

Broader impact

Aligning stakeholder's expectations for target treatment effect **upfront** has potential to give:

- Increased **transparency** and **clarity** with respect to assumptions, data analysis, and inference.
- Clarity about **added value** of drugs: **meaningful** descriptions of treatment effects for licensing and prescribing decisions.
- Clinical trials with designs that are **aligned to agreed objectives**.
- Clear language to describe and discuss different estimands required by different stakeholders.
- More **predictable** regulatory assessment procedures.
- **Reduction in total number of analyses** (primary + secondary + sensitivity).
- **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.

Design trumps analysis.

Don Rubin, American Statistician

Rubin (2008)

Thank you for your attention.

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http://go.roche.com/dss-mco

http://www.kasparrufibach.ch
numbersman77
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Backup

Agenda

Backup: ICH E9(R1) addendum: Why? And what's new?

ICH E9 draft addendum

ICH E9: “Statistical principles for Clinical Trials.”

ICH E9 draft addendum

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1998.

ICH E9 draft addendum

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1998.

Why amend E9?

ICH E9 draft addendum

ICH E9: "Statistical principles for Clinical Trials."

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Why amend E9?

Lack of alignment between trial objectives and reported effect quantification.

Example: Dapagliflozin

ICH E9 working group toy example, Hemmings (2015).

Dapagliflozin:

- Anti-diabetic therapy to treat hyperglycemia.
- Discussed in 2011 in a public advisory committee at **FDA**.

Trial objective: Assess whether drug works compared to placebo.

Example: Dapagliflozin

	Sponsor	FDA
Proposed analysis	Remove data after rescue.	Use all data, irrespective of rescue.
Implied scientific question	Treatment effect of the initially randomized treatments **had no patient received rescue medication**.	Compare treatment **policies** "dapagliflozin + rescue" vs. "control + rescue".

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What is going on?

- Implied objectives / scientific questions of interest **differ for sponsor and regulator**.
- Discussion only at time of **filing**, while this is actually a **design** question!
- Estimand hidden behind the method of estimation / handling of missing data $\Rightarrow$ statistics section defines trial objective!

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- Estimand hidden behind the method of estimation / handling of missing data $\Rightarrow$ statistics section defines trial objective!

"How should we handle missing data?" becomes
"What question are we really interested to answer?"

What is a “treatment effect”?

Treatment effect

Not defined in original E9!

Treatment effect

Not defined in original E9!

How outcome compares to what would have happened to same subject under alternative treatment, e.g. had they

Treatment effect

Not defined in original E9!

How outcome compares to what would have happened to same subject under alternative treatment, e.g. had they

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Potential outcome $\Rightarrow$ causal inference!

Treatment effect

Not defined in original E9!

How outcome compares to what would have happened to same subject under alternative treatment, e.g. had they

- **not** received treatment,
- received a **different** treatment.

Potential outcome $\Rightarrow$ causal inference!

Estimate average treatment effect from **randomized clinical trial**.

Understanding treatment effects

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- Multiple definitions of **treatment effect**.

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- Different definitions addressing **different scientific questions**.

Understanding treatment effects

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- Not all equally acceptable for **regulatory decision making**.

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- Multiple definitions of **treatment effect**.
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- Not all alternatives can be reliably estimated! **Iterative** process of estimand - estimator definition.

Understanding treatment effects

- Multiple definitions of **treatment effect**.
- Different definitions addressing **different scientific questions**.
- Not all equally acceptable for **regulatory decision making**.
- Not all alternatives can be reliably estimated! **Iterative** process of estimand - estimator definition.
- Stakeholders: regulators, HTA / payers, phyisicians, patients $\Rightarrow$ all need to **make decisions**.

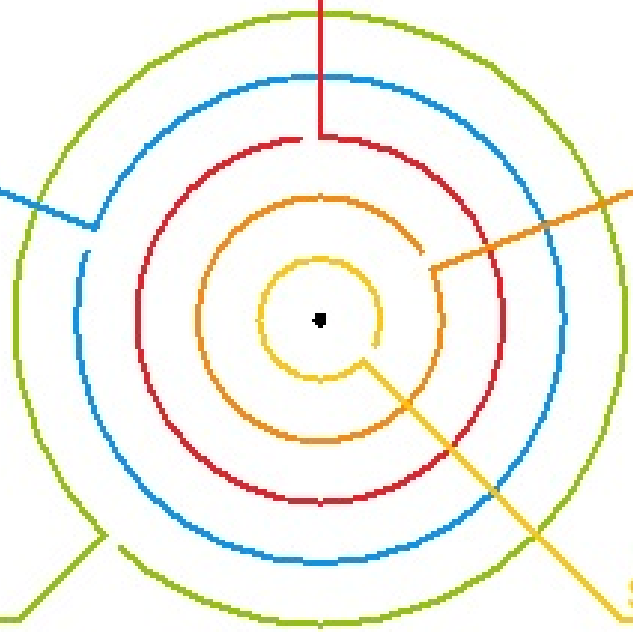
How does the addendum fix this?

How does the addendum fix this?

More precise definition of trial objective
$\Rightarrow$ estimand!

ESTIMAND

TARGET OF ESTIMATION



VARIABLE

The variable (or endpoint) to be obtained for each patient

POPULATION

The population of patients targeted by the clinical question

INTERCURRENT EVENTS

Other intercurrent events (not already addressed by treatment, population, and variable) and how they are addressed

TREATMENT

The treatment condition of interest

SUMMARY

A population-level summary for the variable which provides a basis for treatment comparison

Objective pre- and post-addendum

Pre:

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Estimand follows from precise trial objective (or vice-versa).

Agenda

Backup: Industry working group *Estimands in oncology*

Industry working group on estimands in oncology:

- Founded February 2018.
- Represents industry in Europe and US:
  - European special interest group "Estimands in oncology", sponsored by PSI and EFSPI.
  - ASA scientific working group of ASA biopharmaceutical section.
- **77** members (30 EU + 38 US + 9 Asia) representing **37** companies / institutions.
- Regularly interacts with **8 health authorities**.
- Presentations, webinars, papers.

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janssen
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AstraZeneca
BeiGene
IQVIA
BAYER
Takeda
Incyte
astellas
SERVIER
MODUS OUTCOMES
MERCK
PPD
NEKTAR
Merus battling cancer
CLINICAL OUTCOMES SOLUTIONS
Innovative science to capture the patient voice
stabu ro
Statistical Consulting
AMGEN
ICON
A Symbol of Excellence
Boehringer Ingelheim
phastar
Adelphi
ADELPHI VALUES
Daiichi-Sankyo
MERCK SERONO
zai Lab
Evidera
Bristol Myers Squibb
Genmab
CANCER RESEARCH UK
BIRMINGHAM CANCER RESEARCH UK CLINICAL TRIALS UNIT
UNIVERSITY OF BIRMINGHAM

Papers

Published:

- Lawrance *et al.* (2020): What is an estimand & how does it relate to quantifying the effect of treatment on patient-reported quality of life outcomes in clinical trials. **link**
- Degtyarev *et al.* (2020): Assessing the impact of COVID-19 on the objective and analysis of oncology clinical trials - application of the estimand framework. **link**
- Casey *et al.* (2021): Estimand framework: Are we asking the right question? A case study in the solid tumor setting. **link**
- Sun *et al.* (2021): Estimands in Hematology Trials. **link**
- Manitz *et al.* (2021): Estimands in clinical trials with treatment switching. **link**
- Bornkamp *et al.* (2021): Principal Stratum Strategy: Potential Role in Drug Development. **link** (incl. markdown file with code).
- Hampson *et al.* (2021): Comment on FDA paper on *Biostatistical Considerations When Using RWD and RWE in Clinical Studies for Regulatory Purposes.* **link**

More papers under preparation.

Task forces

- Estimands engagement.
- Principal stratification in clinical trials.
- Patient-reported outcomes.
- Duration of responses.
- Quantification of follow-up.
- Real-world data and estimands.
- Conditional vs. marginal effects.
- Time to event endpoints with prognostic or predictive biomarker subgroups.

Agenda

Backup: 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)

Principal stratification:

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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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"Subgroup" built by post-randomization event!

How can we make valid causal statements?

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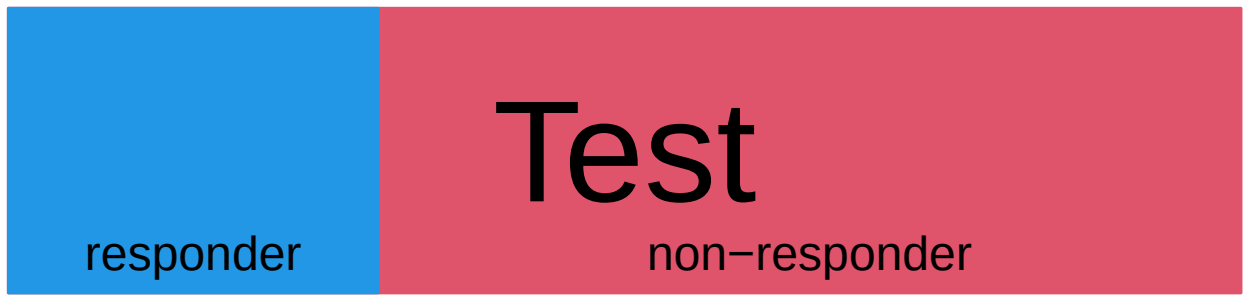
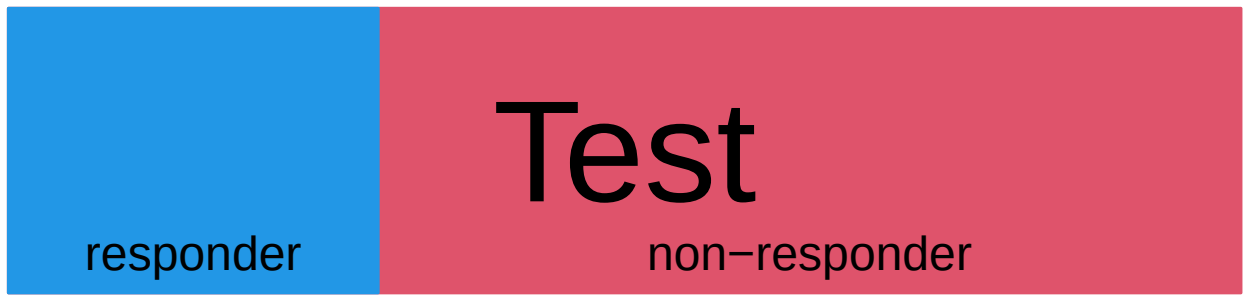
Need "matched control patients"!


Test


Control


Test
responder
non−responder



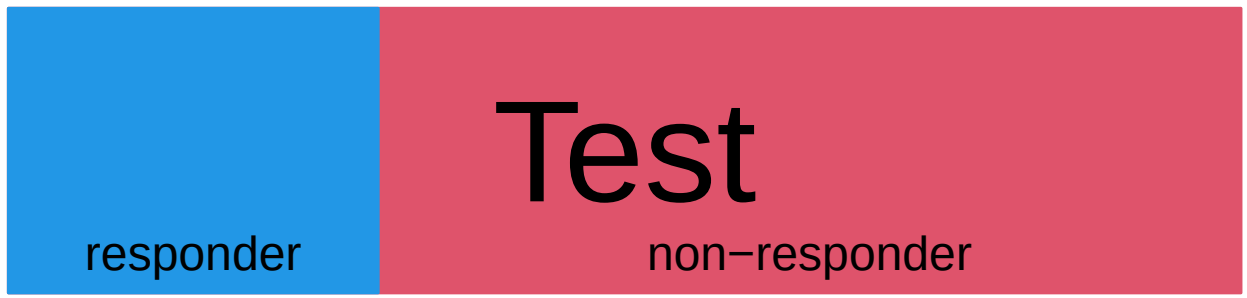
Patients who respond
if randomized to Test
had they received control

Test

Control

Test

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

H.L. Mencken, American Journalist

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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 experimental drug	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).

CAR-T example - see later!

OS / PFS by response.

Potential outcomes and principal stratification

$$Z := \begin{cases} 1 & \text{test treatment} \\ 0 & \text{control treatment.} \end{cases}$$

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

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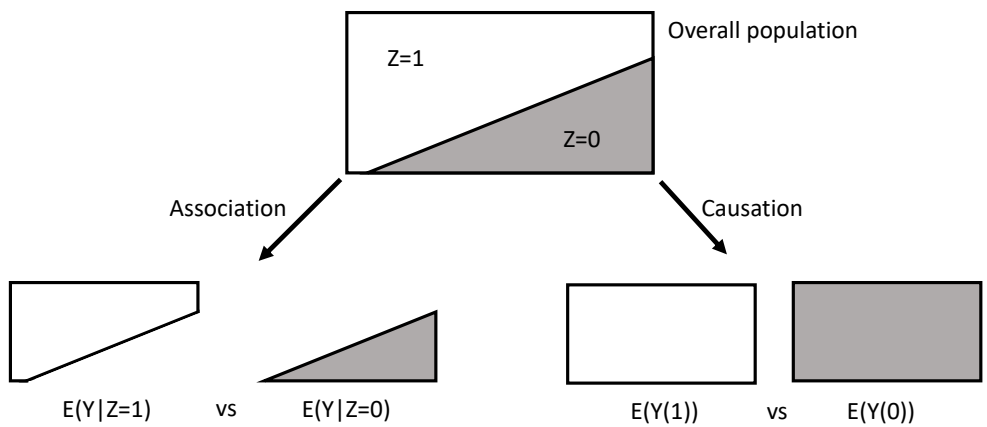

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- Estimates treatment effect in principal stratum $\{S(1) = 1\} \cap \{S(0) = 1\}$ assuming $S(1) = S(0) \Rightarrow$ response not treatment related. Assumption quite strong and **rarely justified**!

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.
- S: occurrence of ADA at x weeks, say $x = 4$.
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	ADA+ under control	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**:

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

Backup: Subgroups by post-randomization event - principal stratification #98 /

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.

Sensitivity analyses!

Assumptions for estimation (see backup) **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

Conclusions principal stratification

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DOI: 10.1002/pst.2104

MAIN PAPER

Principal stratum strategy: Potential role in drug development

Björn Bornkamp[1] | Kaspar Rufibach[2] | Jianchang Lin[3] | Yi Liu[4] | Devan V. Mehrotra[5] | Satrajit Roychoudhury[6] | Heinz Schmidli[1] | Yue Shentu[7] | Marcel Wolbers[2]

Bornkamp et al. (2021)

Markdown:

https://oncoestimand.github.io/princ_strat_drug_dev/princ_strat_example.html

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Effective statistician podcast, Björn Bornkamp and Kaspar Rufibach:

https://theeffectivestatistician.com/

a-deep-dive-into-principal-stratification-and-causal-inference

arXiv.org > stat > arXiv:2101.04263

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[Submitted on 12 Jan 2021]

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

Shengchun Kong, Dominik Heinzmann, Sabine Lauer, Tian Lu

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, i.e. 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 non-negligible number of patients in the experimental arm. For this setting, a novel weighted principal stratum approach 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 proposed approach is provided for different types of outcomes, and assumptions allowing for causal conclusions on treatment effect are specified and investigated. Simulations demonstrated that the proposed 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.

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Talk Dominik in BBS seminar: http://bbs.ceb-institute.org/?p=1668

Agenda

Backup: Estimation of average causal effect

Estimation of average causal effect

Key assumptions:

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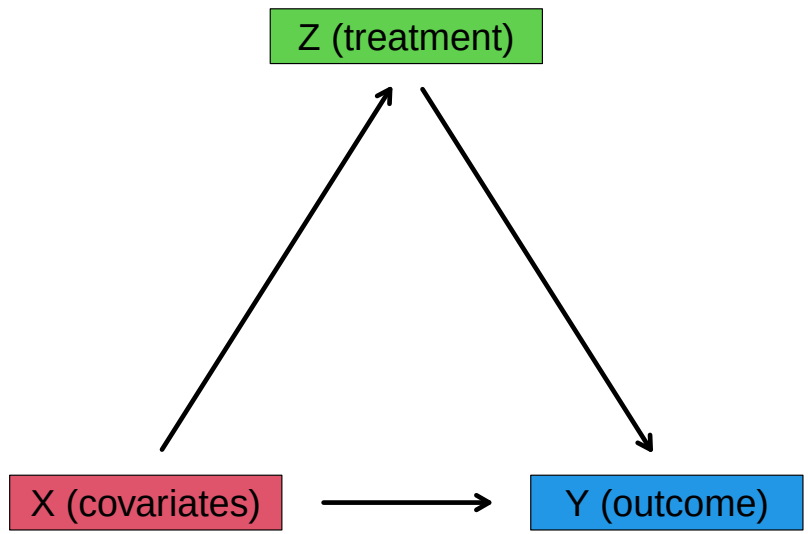

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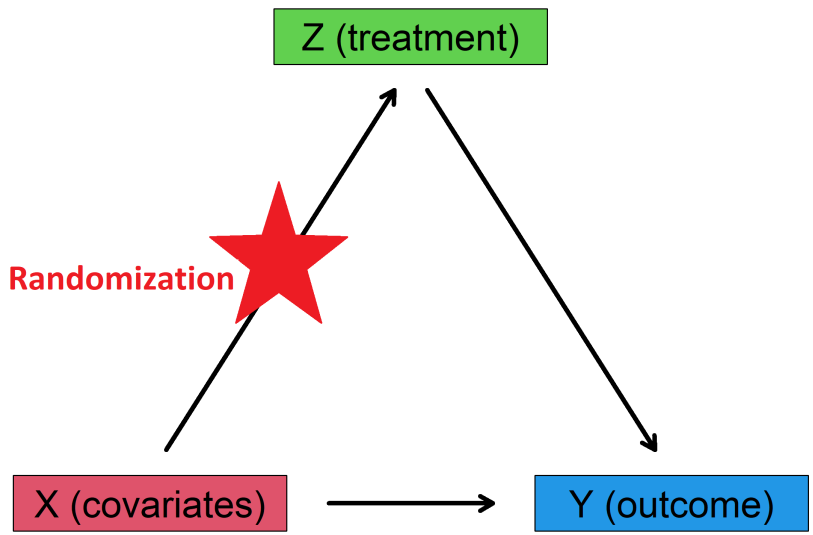

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So - why do we randomize?

- To balance covariates? **NO!**
- Covariates do not appear at all in above computation!
- Randomization generates equal distributions (in both groups) of **potential outcomes**!

For example, one would be extremely hard pressed to find a statistics textbook, even at the graduate level, containing a mathematical proof that randomization indeed produces unbiased estimates of the quantities we wish estimated – i.e., efficacy of treatments or policies.

Judea Pearl, American computer scientist and philosopher

Pearl (2009)

Estimation of average causal effect

Observational study:

Estimation of average causal effect

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- Decision between $Z = 0$ and $Z = 1$ might depend on X (measured or unmeasured).

Estimation of average causal effect

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Backup: 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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Estimation

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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 $S(1) = 1 \Rightarrow$ bottom-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

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.

Estimation under principal ignorability for ADA example

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- Estimate $P(S(1) = 1|X)$ on treatment arm using logistic regression.

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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.

Doing now what patients need next

R version and packages used to generate these slides:

R version: R version 4.1.1 (2021-08-10)

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

Other packages: prodlim

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