Statistical Methodology
Novartis
Basel, Switzerland

Causal reasoning and strategies for defining estimands

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Outline

- ICH E9(R1) – Intercurrent events & the five strategies
- Causal estimands
- Principal Stratum estimand: case studies
- Discussion and Conclusions

Acknowledgements

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- Dan Scharfstein

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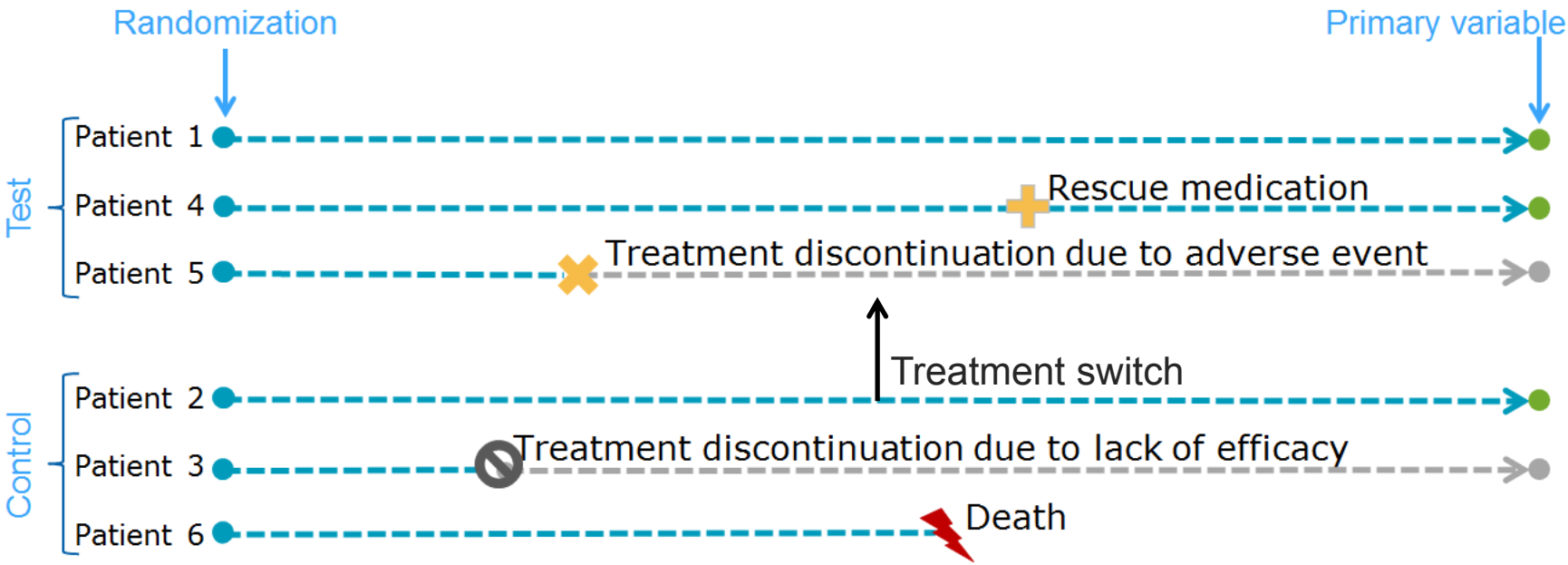
ICH E9(R1) Addendum

Intercurrent events

In clinical trials, one may foresee different types of events after randomization (‘intercurrent events’)



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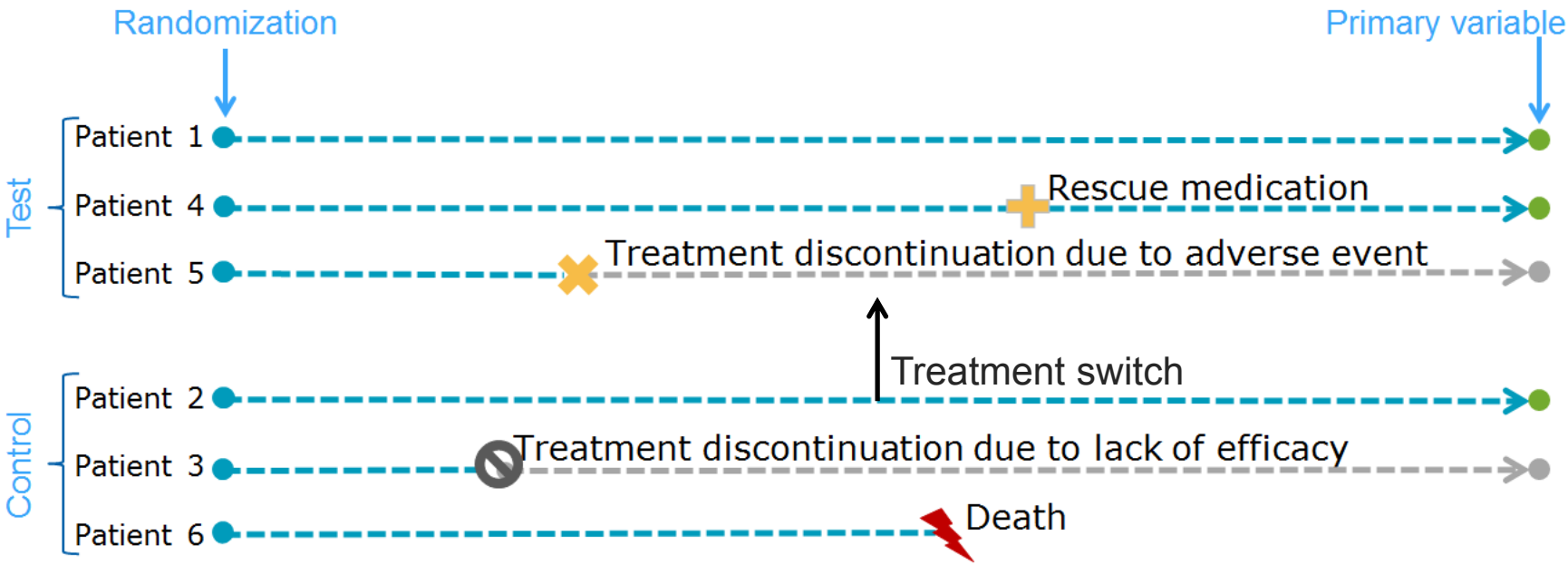
ICH E9(R1) Addendum

Intercurrent events

How to define ‘treatment effect’ in population of interest for primary variable in presence of intercurrent events?



ICH E9(R1) Addendum
Strategies

Five *strategies* for handling each intercurrent event discussed in ICH E9 Addendum.

- *Treatment policy*: Occurrence of intercurrent event ignored;
- *Composite*: Intercurrent event is component of variable;
- *Hypothetical*: Scenario is envisaged in which the intercurrent event would not happen;
- *Principal stratum*: Target population is subpopulation for which intercurrent event would not occur;
- *While on treatment*: Response to treatment prior to the occurrence of the intercurrent event is of interest.

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ICH E9(R1) Addendum

Strategies vs Estimand

Estimand may consider different strategies for each type of intercurrent event

Example

Intercurrent event	**Strategy**
Treatment discontinuation due to AE	Treatment policy
Treatment discontinuation due to lack-of-efficacy	Hypothetical
Death	Composite

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ICH E9(R1) Addendum

Strategies vs Estimand - Type 2 diabetes mellitus

EMA (2018) Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (draft)

Intercurrent event	**Strategy**
Treatment discontinuation	Treatment policy
Use of rescue medication	Hypothetical
Change of background medication	Hypothetical

'... under the assumption that rescue medication, or use of other medications that will influence HbA1c values, was not introduced (hypothetical scenario) ...'

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ICH E9(R1) Addendum

Strategies vs Estimand - Alzheimer's disease

EMA (2018) Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease

8. Confirmatory Trials in Alzheimer´s disease
8.1. Intercurrent events in Alzheimer´s disease
8.1.1. Target of estimation in AD dementia
8.1.2. Target of estimation in the prodromal AD/MCI due to AD or Preclinical AD setting

- **Intercurrent events**: discontinue treatment, initiation of new medication, modification of concomitant symptomatic treatment, vascular/cardiac/metabolic events, death, ...
- **Strategies**: treatment policy, composite, hypothetical, principal stratum

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Causal Estimands

US NAS report

US NAS (2010) The Prevention and Treatment of Missing Data in Clinical Trials

US NAS report - Recommendation 1

‘The trial protocol should explicitly define

a) the objective(s) of the trial;
b) the associated primary outcome or outcomes;
c) how, when, and on whom the outcome or outcomes will be measured;
d) the measures of intervention effects, that is, the **causal estimands** of primary interest.

These measures should be meaningful for all study participants, and estimable with minimal assumptions.’

Term "causal" not used in ICH E9(R1) Addendum, but framework/language aligned with causal reasoning

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Causal Estimands

Causal inference

Causal inference well established science

- Neyman (1923) Agricultural experiments
- Extended by Rubin (1974) to non-randomized studies
- Important contributions by Robins, Pearl, ...

Causal questions expressed using framework of

potential outcomes

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Causal Estimands

Potential outcomes – a thought experiment

Double-blind randomized controlled clinical trial

Seconds before patient Adam is randomized to experimental or control treatment

He will either receive

these pills or these pills

Potential outcomes

Lives 2 years Lives 1 year

Difference between potential outcomes is causal effect

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Causal Estimands

Potential outcomes

- RCT Experimental (E) vs Control (C) treatment
  - Population: patients with cancer
  - Variable: time-to-death Y [years], from time of randomization
  - Intercurrent events ignored (...as a starting point...)

Potential outcome framework*

#	Patient	Y(E)	Y(C)
1	Adam	2	1
2	Bruce	5	7
3	...		

Y(E): how long the patient would live if randomized to E

Y(C): how long the patient would live if randomized to C

**Neyman (1923), Rubin (1974)*

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Causal Estimands

Population causal estimand

Potential outcome framework

#	Patient	Y(E)	Y(C)	Y(E)-Y(C)	
1	Adam	2	1	+1	Individual causal effect
2	Bruce	5	7	-2	
3	...				

Y(E), Y(C): how long the patient would live if randomized to E or C

Population causal estimand, e.g.

$$\text{average}(Y(E) - Y(C)) = \text{average}(Y(E)) - \text{average}(Y(C))$$

Many alternatives, e.g.

- average(log{Y(E)}) - average(log{Y(C)}) Accelerated Life Time
- median(Y(E)) / median(Y(C))

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Causal Estimands

Statistical inference

		Potential outcomes		Observed			
#	Patient	Y(E)	Y(C)	Treatment X	Y	Y(E)	Y(C)
1	Adam	2	1	E	2	2	?
2	Bruce	5	7	C	7	?	7
3	...						

Estimation – key role of randomisation

- Y(E), Y(C) independent of treatment X for randomized controlled trials
- average(Y | X=E) – average(Y | X=C) unbiased estimate of average(Y(E)) – average(Y(C))

Frequentist and Bayesian approaches available for statistical inference

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Causal Estimands

Strategies

ICH E9 Addendum *strategies* for intercurrent events

- *Treatment policy (ITT)*: Occurrence of intercurrent event ignored;
- *Composite*: Intercurrent event is component of variable;
- *Hypothetical*: Scenario is envisaged in which the intercurrent event would not occur;
- *Principal stratum*: Target population is subpopulation for which intercurrent event would not occur;
- *While on treatment*: Response to treatment prior to the occurrence of the intercurrent event is of interest.

Causal language - illustration in RCT setting:

- Experimental (E) vs Control (C) treatment
- Just one intercurrent event

Scharfstein (2017)

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Causal Estimands

Strategies

- Population: Patients with diabetes
- Variable: Y=Change in HbA1c from baseline to 24 weeks [mmol/mol]
- Intercurrent event: R=intake of rescue medication

#	Patient	Y(E)	R(E)	Y(C)	R(C)
1	John	2	no	5	yes
2	Brian	-8	yes	0	yes

- Strategies

a) Treatment-policy/ITT: Y(E) vs Y(C)

e.g. average(Y(E)) – average(Y(C))

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Causal Estimands

Strategies

#	Patient	Y(E)	R(E)	*Y(E,R=no)*	Y(C)	R(C)	*Y(C,R=no)*
1	John	2	no	*2*	5	yes	*7*
2	Brian	-8	yes	*-1*	0	yes	*1*

Hypothetical Y(E,R=no): if rescue medication would not have been allowed

- Strategies
  a) Treatment-policy/ITT: Y(E) vs Y(C)
  b) Hypothetical: Y(E,R=no) vs Y(C,R=no)
  e.g. average(Y(E,R=no)) – average(Y(C,R=no))

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Principal Stratum Estimand

Subgroups

- Treatment effect in specific subgroups guide decisions:
  product labeling, reimbursement, clinical practice
- Yusuf et al (1991) *JAMA*
  - “Proper subgroups": characterized by baseline data
  - “Improper subgroups“: characterized by post-randomization data
- Naive analysis for "improper subgroups“ misleading (post-randomization data are affected by treatment)
- Frangakis and Rubin (2002) *Biometrics*
  - Potential outcomes for post-randomization data
  - Subgroup defined based on potential outcomes
  - "Proper subgroup" as potential outcomes can be handled as baseline covariates

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Principal Stratum Estimand

Case study 1

- Phase 3 study, experimental vs control
  - Patients with previous myocardial infarction and increased inflammation, i.e. high-sensitivity C-reactive protein (hs-CRP) ≥ 2mg/l
  - Primary endpoint: nonfatal MI or stroke, CV death
  - Biomarker: inflammation (hs-CRP)
- Scientific/regulatory questions
  - Treatment effect on primary endpoint ✓
  - Treatment effect on primary endpoint, in *subgroup* of patients which would be biomarker responders at 3 months if assigned to experimental treatment **?**

Ridker et al. (2017) NEJM, Ridker et al. (2018) Lancet

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Principal Stratum Estimand

Case study 1

Formal language

- Treatment X (E vs C)
- Primary clinical endpoint Y (binary)
- Biomarker response Z (0 or 1)

		Potential outcomes			Observed outcomes		
#	Patient	Y(E)	Z(E)	Y(C)	X	Y	Z(E)
1	Adam	1	1	1	E	1	1
2	Bruce	0	0	1	C	1	?
3	Conny	0	0	0	E	0	0
4	Dan	0	1	0	E	0	1
5	Eve	0	1	1	C	1	?

Subgroup of patients which would be biomarker responders if assigned to E

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Principal Stratum Estimand

Case study 1

Treatment X (E vs C)

Primary clinical endpoint Y (binary)

Biomarker response Z (0 or 1)

- Scientific/regulatory questions on treatment effect on
  - Primary endpoint: $P(\ Y(E)\ )\ -\ P(\ Y(C)\ )$
  - Primary endpoint, in subgroup of patients which would be biomarker responders at 3 months if assigned to experimental treatment:

    $P(\ Y(E)\ |\ Z(E)=1\ )\ -\ P(\ Y(C)\ |\ Z(E)=1\ )$

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Principal Stratum Estimand

Case study 2

- Phase 3 study, experimental vs control
  - Primary endpoint (binary)
  - Clinical event (binary)
- Occurrence of clinical event may impact value of primary endpoint
- Scientific/regulatory questions
  - Treatment effect on primary endpoint ✓
  - Treatment effect on clinical event (secondary endpoint) ✓
  - Treatment effect on primary endpoint, in *subgroup* of patients where clinical event would not occur (regardless of treatment assignment) **?**

Magnusson et al. (2018)

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Principal Stratum Estimand

Case study 2

- Formal language
  - Treatment X (E vs C)
  - Primary endpoint Y (0 or 1)
  - Clinical event Z (0 or 1)
- Scientific/regulatory questions on treatment effect on
  - Primary endpoint: P(Y(E)) - P(Y(C))
  - Clinicel event: P(Z(E)) - P(Z(C))
  - Primary endpoint, in subgroup of patients where Z would not occur regardless of treatment assignment:

$$P(Y(E) \mid Z(E)=Z(C)=0) - P(Y(C) \mid Z(E)=Z(C)=0)$$

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Discussion

- Traditional estimand

  (Complex) model including treatment effect parameter θ

- Causal estimand

  Marginal comparison of potential outcomes: e.g. Y(E) vs Y(C)

- Advantages of causal estimand formulation
  - Potential outcome framework natural for medical doctors
    'What happens to my patient if I give him treatment E vs treatment C ?'
  - Understandable for patients
  - No statistical model needed to discuss with clinicans/patients
  - Easier to think about how to account for intercurrent events

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Discussion

Role of statistical models

- Traditional estimand is model parameter, which is not interpretable if model is not adequate
- Causal estimand is model-free
- However, models can/should be used for inference!

Example

Y = Change in HbA1c from baseline to 24 weeks

Causal estimand average(Y(E)) - average(Y(C))

To obtain point estimates/CI/p-value/posterior distribution, one could use e.g. a normal distribution model

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Discussion

- Causal reasoning
  - Provides guidance on which estimands make sense
  - 'No causation without manipulation' Holland and Rubin, 1986

Example – hypothetical estimand

Diabetes patients, change in HbA1c

- Intercurrent event: R=intake of rescue medication

  Y(E,R=no): if rescue medication would not have been allowed OK
- Intercurrent event: R=Discontinuation due to AE

  Y(E,R=no): if patients would not have discontinued due to AE ?
- Intercurrent event: R=Death

  Y(E,R=no): if patients would not die ???

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Conclusions

- ICH E9(R1) Addendum should lead to more transparent discussions between sponsor and regulators on trial objectives and target of estimation
- Opportunity to reconsider appropriate estimands for health technology assessments
- Causal reasoning is key for an appropriate choice of the estimand
- Potential outcome framework useful for interactions between statisticians, clinicians ... and patients.

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