Global Drug Development Analytics

Principal Stratum Strategy: Potential Role in Drug Development

Bornkamp, Björn

BBS Webinar: RCTs meeting causal inference

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Acknowledgements

Kaspar Rufibach, Heinz Schmidli &

Causal subteam of the oncology estimand working group (oncoestimand.org)

Causal Subteam Paper on principal stratum
https://arxiv.org/pdf/2008.05406.pdf

Principal Stratum Strategy: Potential Role in Drug Development

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Outline

Principal Stratum Strategy

Practical Relevance

Conclusions

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ICH E9(R1): Principal Stratum Strategy

"... 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. ..."

Example

"... a toxicity might prevent some patients from continuing the test treatment, but it would be desired to know the treatment effect among patients who are able to tolerate the test treatment. ..."

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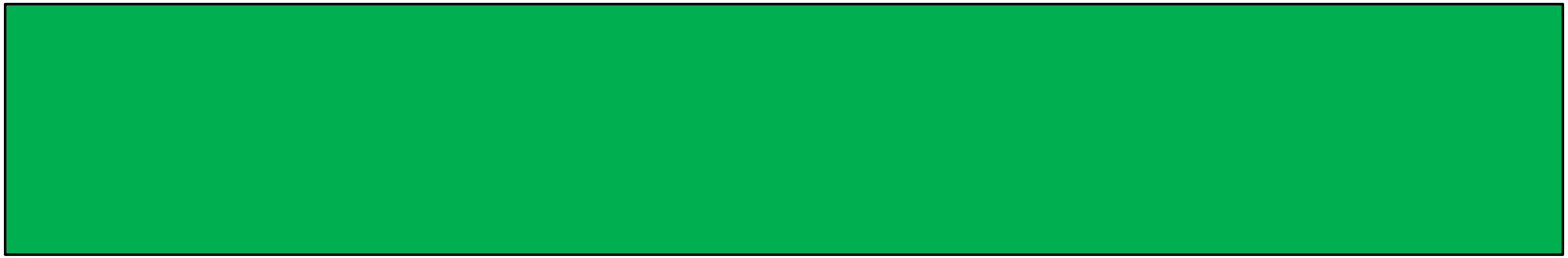
Principal Stratum Effect: Definition

Patients randomized to test treatment



Patients randomized to control treatment

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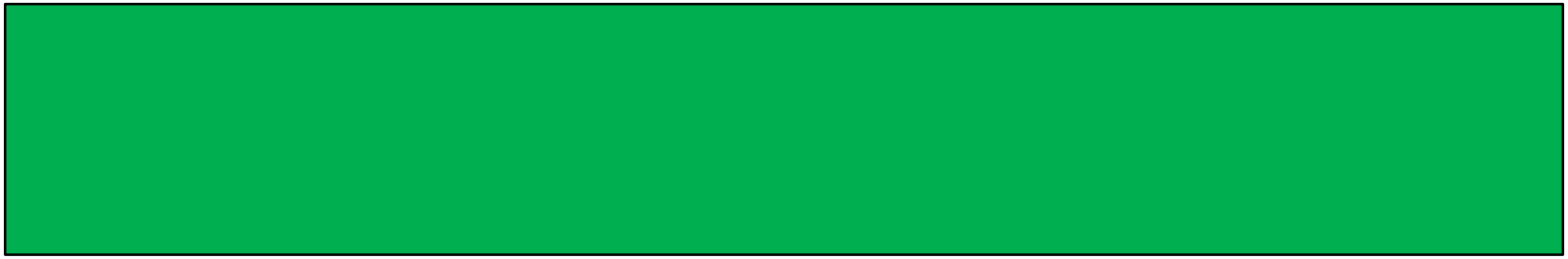
Principal Stratum Effect: Definition

Patients randomized to test treatment



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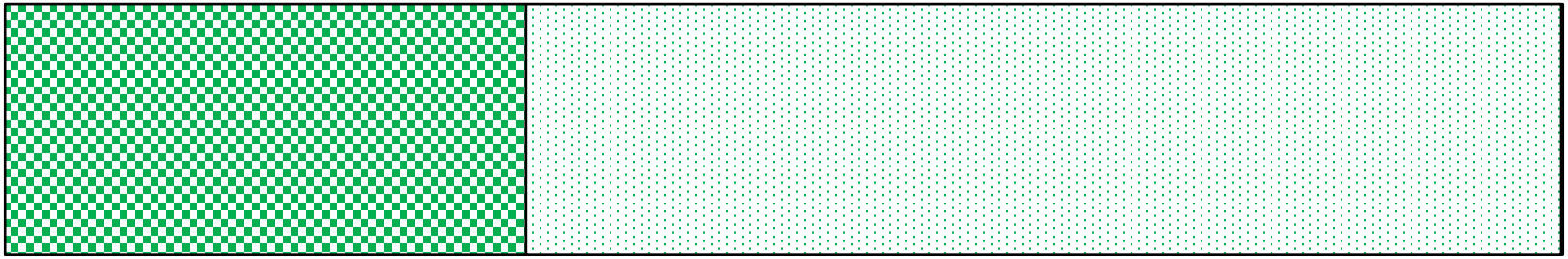
Principal Stratum Effect: Definition

Patients randomized to test treatment



Patients with toxicity (on test treatment)

Patients without toxicity (on test treatment)

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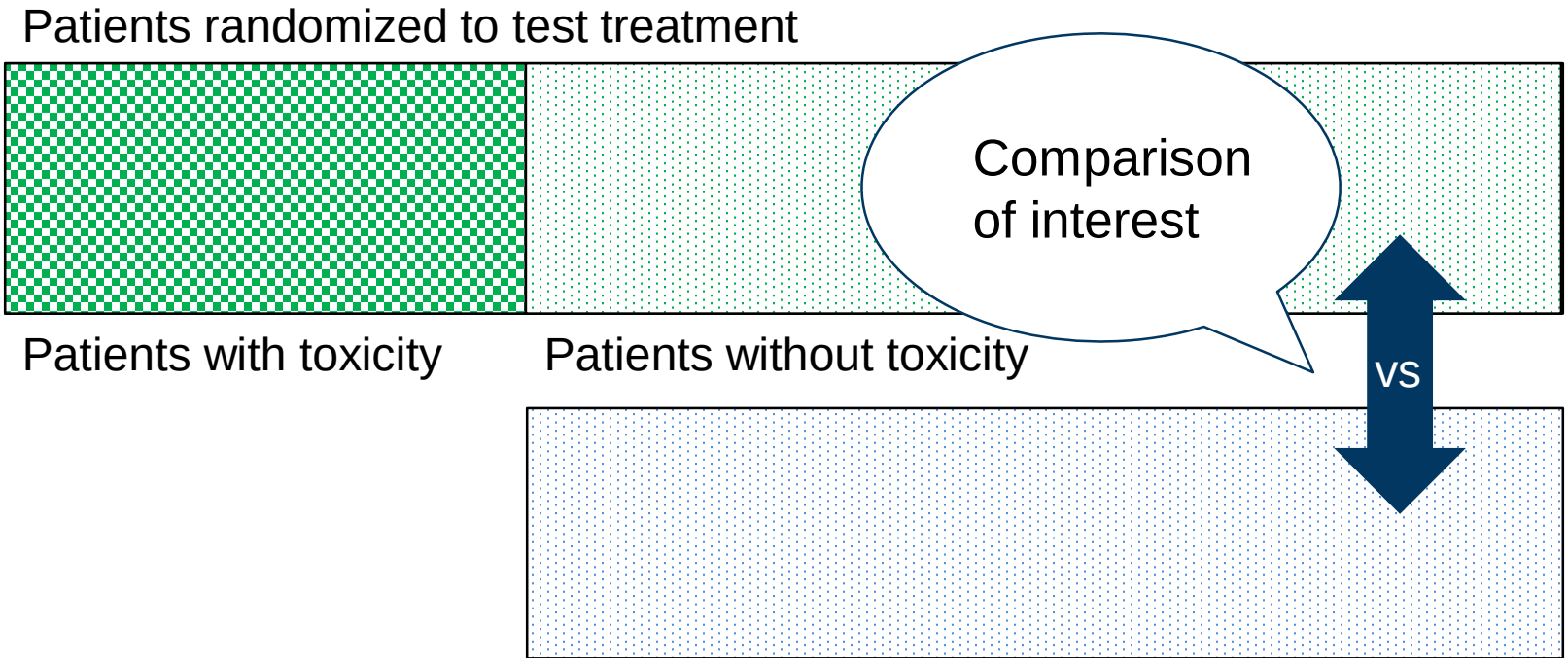
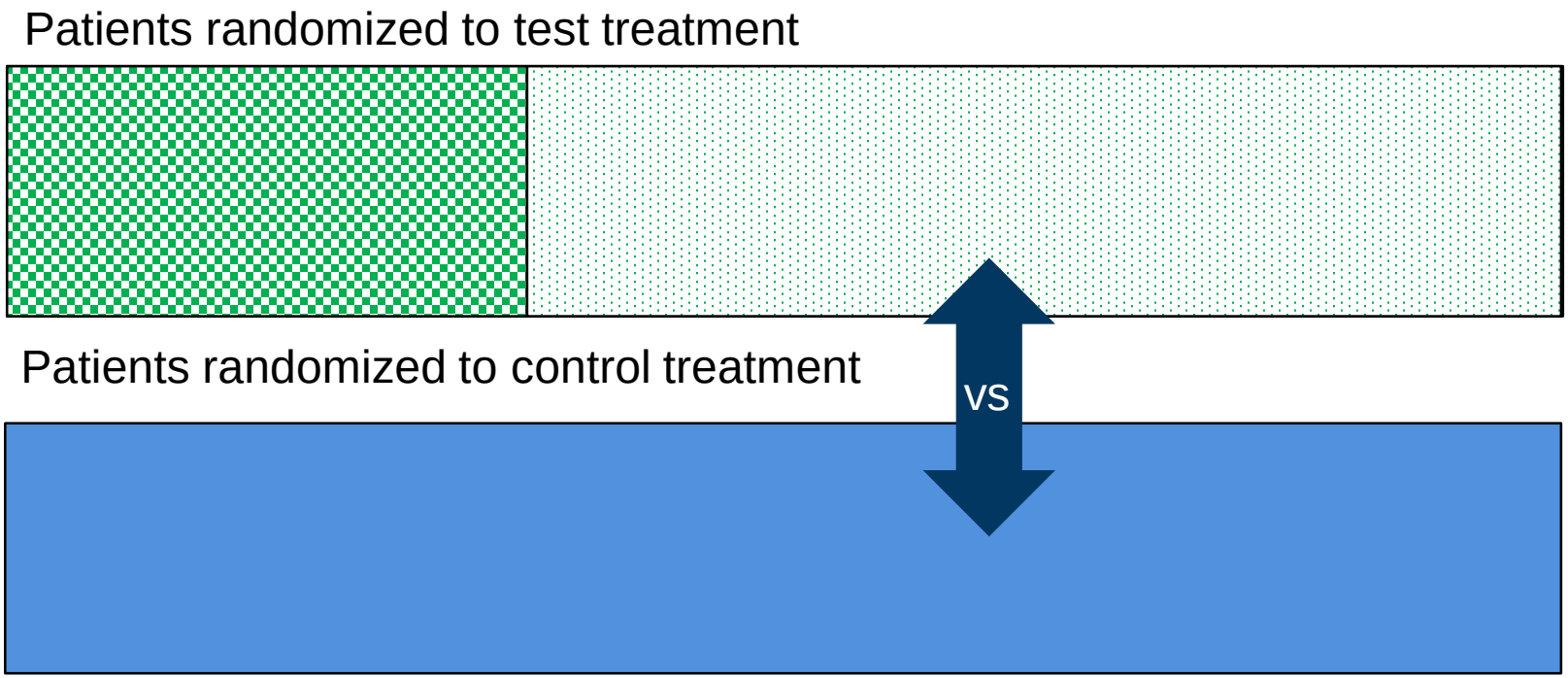
Principal Stratum Effect: Definition



Analysis 1: Not targeting principal stratum effect



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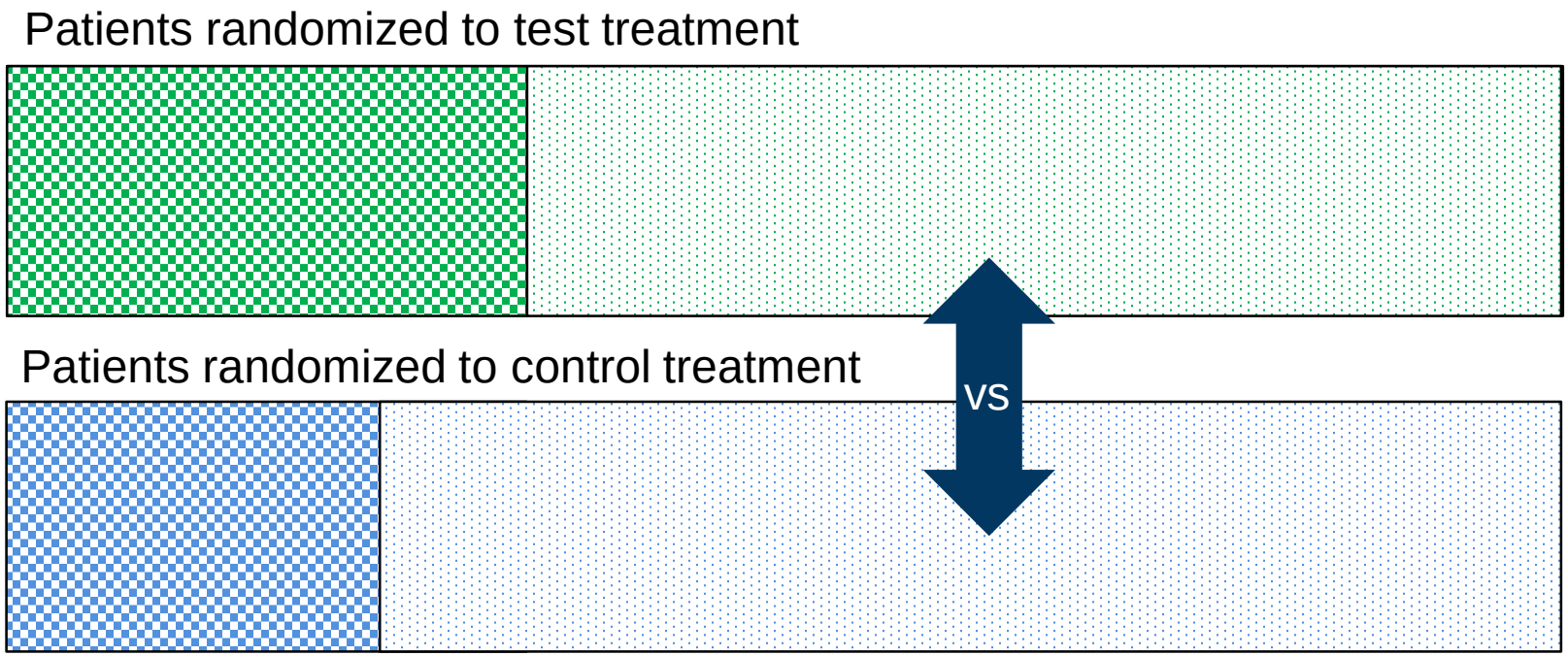
Analysis 2: Not targeting principal stratum effect



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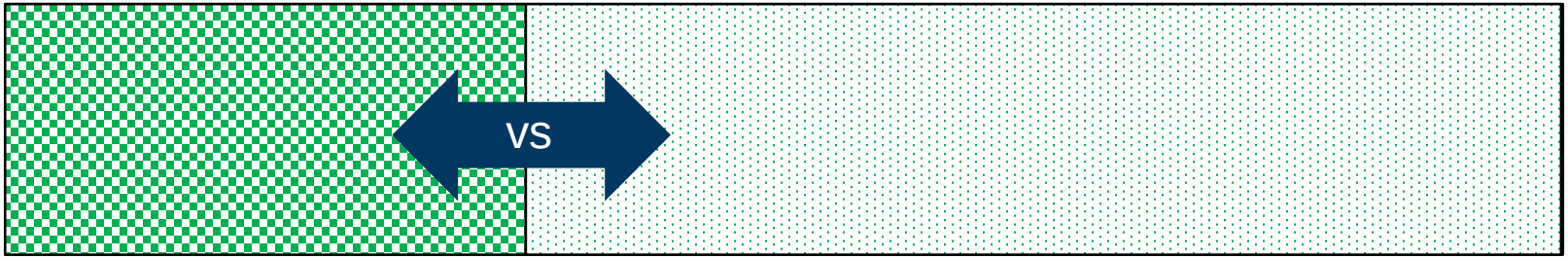
Analysis 3: Not targeting principal stratum effect

Patients randomized to test treatment



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Some possible assumptions for estimation of principal stratum effects

- No assumption
  - Proportion of patients with toxicity on test treatment can be estimated: Best/worst case scenario on correct group of control patients
- Weak assumptions
  - Scientific model with weakly informative prior information
- Monotonicity
  - Patients with toxicity on control arm would also have had a toxicity on treatment arm then best/worst case scenario on correct group of control patients
- Principal ignorability
  - All patient characteristics predictive of outcome on control treatment & toxicity on test treatment → Match, adjust, weight control arm patients to find „right control group“
- Unverifiable assumptions → ***Scientific understanding & Sensitivity Analyses***

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Practical Relevance

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Efficacy and Safety Outcomes in Patients With Advanced Melanoma Who Discontinued Treatment With Nivolumab and Ipilimumab Because of Adverse Events: A Pooled Analysis of Randomized Phase II and III Trials

Outcomes: progression-free survival, overall survival
Intercurrent event: Treatment discontinuation due to AE

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Antidrug Antibodies Against Immune Checkpoint Blockers: Impairment of Drug Efficacy or Indication of Immune Activation?

Diego Enrico[1,2], Angelo Paci[1,3,4], Nathalie Chaput[1,3,5], Eleni Karamouza[1,6], and Benjamin Besse[1,2,7]

ABSTRACT

The generation of antibodies following exposure to therapeutic drugs has been widely studied, however in oncology, data in relation to their clinical relevance are limited. Antidrug antibodies (ADAs) can cause a decrease in the amount of drug available, resulting in some cases in decreased antitumor activity and a consequent impact on clinical outcomes. Several immunologic factors can influence the development of ADAs, and in addition, the sensitivity of the different testing methods used in different studies can vary, representing an additional potential confounding factor. The reported frequency of ADA-positive patients following treatment with immune checkpoint inhibitors varies from as low as 1.5% for pembrolizumab to 54% for atezolizumab. This latter drug is the only immune checkpoint inhibitor to have undergone an expanded analysis of the clinical implications of ADAs, but with discordant results. Given that immune checkpoint inhibitors can modify the immune response and potentially impact ADA formation, data from published as well as prospective trials need to be evaluated for a better understanding of the clinical implications of ADAs in this setting.

Outcomes: overall survival
Intercurrent event: Development of ADAs

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Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial

*Paul M Ridker, Jean G MacFadyen, Brendan M Everett, Peter Libby, Tom Thuren, Robert J Glynn, on behalf of the CANTOS Trial Group**

Summary

Background Canakinumab, a monoclonal antibody targeting interleukin-1β, reduces inflammation and cardiovascular event rates with no effect on lipid concentrations. However, it is uncertain which patient groups benefit the most from treatment and whether reductions in the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) correlate with clinical benefits for individual patients.

Lancet 2018; 391: 319–28

Published Online
November 13, 2017
http://dx.doi.org/10.1016/S0140-6736(17)32814-3

It is uncertain which patients gain the greatest cardiovascular benefit when treated with the anti-inflammatory agent

of

Outcomes: Major cardiovascular events (MACE)
Intercurrent event: hsCRP response at month 3

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The Combination of Exposure-Response and Case-Control Analyses in Regulatory Decision Making

The Journal of Clinical Pharmacology
53(2) 160–166
© The Author(s) 2012
DOI: 10.1177/0091270012445206

Abstract

To reduce the bias introduced by confounding risk factors, a case-control comparison was incorporated in the exposure-response (ER) analysis to evaluate the recommended dosing regimen for trastuzumab in a pivotal trial. Results of Kaplan-Meier survival analysis suggest that patients with metastatic gastric cancer (mGC) in the lowest quartile trough concentrations of trastuzumab in cycle 1 ($C_{min,1}$) had shorter overall survival (OS) than did those in other quartiles. The result of the case-matched control comparison suggests that adjusting for these risk factors, patients with the lowest quartile of trastuzumab exposure did not benefit from addition of trastuzumab treatment to chemotherapy. The identified subgroup without survival benefit and the ER relationship support the recommendation on conducting clinical trials to identify a treatment regimen with greater exposure and acceptable safety profiles and to prospectively evaluate whether this treatment regimen will result in survival benefit for the identified subgroup.

Outcomes: Overall survival
Intercurrent event: low trough drug concentration in cycle I

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 17, 2003 VOL. 349 NO. 3

The Influence of Finasteride on the Development of Prostate Cancer

RESULTS

Prostate cancer was detected in 803 of the 4368 men in the finasteride group who had data for the final analysis (18.4 percent) and 1147 of the 4692 men in the placebo group who had such data (24.4 percent), for a 24.8 percent reduction in prevalence over the seven-year period (95 percent confidence interval, 18.6 to 30.6 percent; P<0.001). Tumors of Gleason grade 7, 8, 9, or 10 were more common in the finasteride group (280 of 757 tumors [37.0 percent], or 6.4 percent of the 4368 men included in the final analysis) than in the placebo group (237 of 1068 tumors [22.2 percent], P<0.001 for the comparison between groups; or 5.1 percent of the 4692 men included in the final analysis, P=0.005 for the comparison between groups). Sexual side effects were more common in finasteride-treated men, whereas urinary symptoms were more common in men receiving placebo.

CONCLUSIONS

Finasteride prevents or delays the appearance of prostate cancer, but this possible benefit and a reduced risk of urinary problems must be weighed against sexual side effects and the increased risk of high-grade prostate cancer.

Outcome: Tumor Gleason grade >= 7 (binary)

Intercurrent event: Development of prostate cancer

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16 years later...

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Long-Term Effects of Finasteride on Prostate Cancer Mortality

and anxiety.[5] Finasteride is a generic agent that is used to treat lower urinary tract symptoms, prevents complications from these symptoms, and prevents prostate cancer. The early concerns regarding an association between finasteride and an increased risk of high-grade prostate cancer have not been borne out.

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Guideline on the evaluation of anticancer medicinal products in man

7.6. Methodological considerations 29
7.6.1. Adaptive design 30
7.6.2. Interim analyses 30
7.6.3. Time to event analyses and assessment of response and progression 30
7.6.4. Non-inferiority studies 31
7.6.5. Analyses based on a grouping of patients on an outcome of treatment 31
7.6.6. Studies in small study populations, very rare tumours 31
7.6.7. Use of external control 32
7.7. Special populations 32
7.7.1. Elderly and frail patients 32
7.7.2. Children 33
7.7.3. Gender 33
7.7.4. Patients with impaired organ function 33

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DOI: 10.1002/sim.8333

RESEARCH ARTICLE

WILEY Statistics in Medicine

Bayesian inference for a principal stratum estimand to assess the treatment effect in a subgroup characterized by postrandomization event occurrence

Baldur P. Magnusson[1] | Heinz Schmidli[1] | Nicolas Rouyrre[1] |
2 | Daniel O. Scharfstein[2]

EXPAND was a randomized, double-blind, placebo-controlled, event- and exposure-driven phase 3 study evaluating the efficacy of siponimod in patients with SPMS.[16] 1651 patients were randomized in a 2:1 ratio to receive once-daily 2 mg siponimod or placebo. The primary objective was to demonstrate efficacy of siponimod relative to placebo in delaying the time to 3-month confirmed disability progression (CDP) as measured by the Expanded Disability Status Scale (EDSS). The EDSS is an ordinal scale used for assessing neurologic impairment in MS based on a neurological examination. It combines scores in seven functional systems and an ambulation score, and ranges from 0 (no impairment) to 10 (death due to MS). Three-month CDP is defined by a prespecified increase from the EDSS baseline that is subsequently sustained for at least 3 months. The study achieved its objective with an estimated hazard ratio of 0.79 (95% CI, 0.65-0.95).

Outcome: Confirmed disability progression (binary)
Intercurrent event: Relapse

g relapsing-remitting disease stage, some
s experience an increased EDSS score from
e during a relapse). As expected based on
with a rate ratio of 0.45 (95% CI, 0.34-0.59).
This raised the question of siponimod's ability to delay CDP unrelated to its effect on relapses. Of particular interest was the effect of siponimod among the subgroup of patients for whom relapses would be absent during the study.

Summary

- Many examples of practical relevance in drug development
- Often not related to primary objective of the trial
  - But important follow-up questions to characterize how the treatment effects vary across subgroups defined by intercurrent events
- Can have implications on how a drug is used in practice and labeling

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Conclusions

- Principal stratum strategy in these situations
  - complex question → complex analysis
  - but more appropriate analyses (more transparent & plausible assumptions)
    - with principal stratum strategy at least clear „what to estimate“
  - avoid „simple analyses“ with unclear interpretation (likely to get interpreted incorrectly)
- Assumptions needed and may be very situation specific (no default approach)
  - Need for scientific basis of assumptions
  - Need to perform sensitivity analyses
    - Directly modifying assumptions

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References

- Principal stratum
  - Frangakis, C. E. and Rubin, D. B. (2002). Principal stratification in causal inference. Biometrics 58 21–29.
  - Feller, A., Mealli, F. and Miratrix, L. (2017). Principal score methods: Assumptions, extensions, and practical considerations. Journal of Educational and Behavioral Statistics 42 726–758.
- Causal mediation analysis & relationship to principal stratum
  - Baccini, M., Mattei, A. and Mealli, F. (2017). Bayesian inference for causal mechanisms with application to a randomized study for postoperative pain control. Biostatistics 18 605–617.
  - VanderWeele, T. J. (2008). Simple relations between principal stratification and direct and indirect effects. Statistics & Probability Letters 78 2957–2962.

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Thank you

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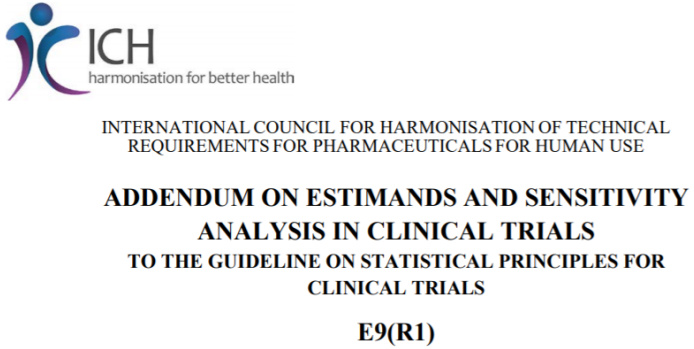
ICH E9(R1) guideline: Intercurrent Events (IE)



"... Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. ..."

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ICH E9(R1): Intercurrent event strategies to define estimand

- Treatment policy
  - Effect regardless of IE → IE becomes part of „treatment attribute“
- Hypothetical
  - Effect in hypothetical scenario where IE would not occur
- Composite
  - Effect on a composite variable, where IE is part of the variable
- While-on-treatment
  - Effect up to IE is considered of interest (modifies variable, i.e. observation time per patient)

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Markdown file to example R implementations

- https://oncoestimand.github.io/princ_strat_drug_dev/princ_strat_example.html
- See https://arxiv.org/pdf/2008.05406.pdf for more details

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