Estimation of Principal Stratum Effects, an Overview and Potential Applications in Oncology

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Estimands in Oncology: Need for the Industry Working Group

- increased transparency on treatment effect of interest considered as important goal of the ICH E9 addendum

But **what if the same estimand is described differently by sponsors** in protocols and publications?

→ **confusion for HA, payers, physicians and patients**

→ **inconsistent labels**

→ more HA questions on estimands creating perception of estimand topic being rather a burden

- main **purpose of the Working Group**:
  - **ensure common understanding and consistent definitions for key estimands in Oncology across industry**
  - share experience and discuss estimands, intercurrent events and the used sensitivity analyses in Oncology

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Oncology Estimands WG

- Initiated and led by Evgeny Degtyarev (Novartis) and Kaspar Rufibach (Roche), first TC Feb 2018
- 32 members (14 from Europe and 18 from US) representing 20 companies

Causal-Subteam

- Kaspar Rufibach (Roche), lead
- Vera Beckers (Abbvie)
- Björn Bornkamp (Novartis)
- Audrey Boruvka (Roche)
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Agenda

- Clinical questions
- Estimation of principal stratum effects
- Criticisms
- Summary

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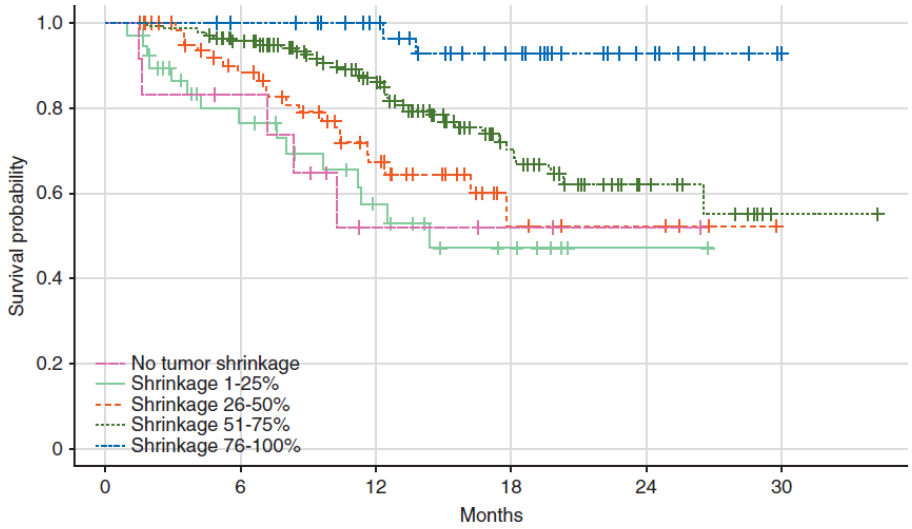
Clinical questions

- Short term tumour shrinkage versus overall survival
  - Short term tumour shrinkage can be a good predictor of overall survival
- What is the treatment effect versus control (on overall survival) in patients that have a tumour shrinkage < X % at Y weeks if on the investigational treatment?



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Clinical questions

- Biologic treatments and antidrug antibodies (ADA)
  - For biologic treatments (e.g. cancer immunotherapies) ADAs might form and may (or may not) have a neutralizing effect on the treatment
- What is the treatment effect versus control (e.g. on overall survival) in patients that develop ADAs if on the investigational treatment?
  - Note the control treatment might be a non-biologic drug, so that ADAs by definition will not form

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Clinical questions

- Commonality
  - Evaluate the treatment effect in the subgroup of patients where a specific post-randomization event would (or would not) occur
  - Challenge: Post-randomization event itself may be affected by treatment
    - Randomization cannot be relied upon to ensure comparable groups on investigational treatment and control → Selection bias
- Class of questions is quite frequent in oncology
  - See Section 7.6.5 of the EMA anticancer guidance on „Analyses based on a grouping of patients on an outcome of treatment“
    - Highlights problematic nature of naive analyses
    - Encourages search for „unexpected findings“ based on such exploratory analyses (by each treatment arm; not formally comparing arms due to non-randomized nature)

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Principal Stratification Estimands

- Concept introduced in Frangakis & Rubin (2002)
  - Introduce potential outcomes (binary) S(0) and S(1) for **every** patient in the trial
    - Even though just one of the two is observed for every patient
  - Determine treatment effect in subset(s) (principal strata) of population defined by S(0) and S(1) → leads to 4 principal strata

S – occurence of postbaseline event
S(0) – potential outcome control
S(1) – potential outcome treatment

- Example
  - Suppose we are interested in the treatment effect in patients, who develop ADAs on treatment (have S(1) = 1) (union of 2 principal strata)
  - For patients on treatment we observe S(1)
  - Problem: For patients on control we do not observe S(1)

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Principal Stratification Estimands

- By itself just provides a way to formulate the question/problem not the solution
- Why is this of any help then?
  - Provides a clear inferential target (treatment effect in principal strata)
  - Easier to discuss assumptions etc if inferential target is clear
- Determination of treatment effects in principal strata requires assumptions!
  - E.g. Principal stratum membership is not observed
- Let‘s illustrate with the ADA example in more detail

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ADA example in more detail

- Quantity of interest?
  - Survival time under treatment or control for patients who would develop ADAs if given active treatment (S(1)=1).

Potential outcomes
T(z) – Potential survival time
S(z) – ADA presence post-baseline

- In potential outcome notation: Compare

$$T(1)|\{S(1) = 1\} \text{ versus } T(0)|\{S(1) = 1\}$$

  - e.g. estimate survival functions $P(T(1) > t|S(1) = 1)$ and $P(T(0) > t|S(1) = 1)$ and derive a summary measure based on those

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ADA example

- In potential outcome notation: Compare
  $$T(1)|\{S(1) = 1\} \text{ versus } T(0)|\{S(1) = 1\}$$
  - e.g. estimate survival functions $P(T(1) > t|S(1) = 1)$ and $P(T(0) > t|S(1) = 1)$ and derive a summary measure based on those
- Easy to derive an estimate for $P(T(1) > t|S(1) = 1)$: Observed on treatment arm
- How to derive estimate of $P(T(0) > t|S(1) = 1)$?
  - No one-size-fits-all solution in the Frangakis and Rubin (2002) paper

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ADA example: Full Bayesian estimation

- We know that we observe a mixture of patients on the control arm

$$p(T(0)) = \pi\, p(T(0)|S(1) = 1) + (1 - \pi)\, p(T(0)|S(1) = 0)$$

  - $\pi = P(S(1) = 1)$ can be estimated from the treatment arm

- Densities
  - $p(T(0)|S(1) = 1)$ and $p(T(0)|S(1) = 0)$ not identified based on the data without further (e.g. parametric) assumptions

  → even for „infinite“ sample size, likelihood will not contract to a single point

- Binary outcome data
  - Even parametric assumptions not sufficient
  - Magnusson et al. (2018) utilize fully Bayesian approach for identification: Proper prior leads to a proper posterior distribution

    → Need to evaluate impact of „weakly-informative“ priors carefully

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ADA example: Utilizing covariates

- Assume one can find all covariates X such that
  - Conditional on covariates X, T(0) and S(1) are independent: $T(0) \perp S(1) \mid X$
    - Principal ignorability, see Ding et al. 2017, Feller et al. 2017
    - Similar to assumptions used in propensity score analyses
  - If this is true the conditional distribution $p(T(0) \mid S(1), X) = p(T(0) \mid X)$
- Estimation (see also Bornkamp & Bermann, 2019)
  - Estimate $p(T(0) \mid X)$ on control group, average with respect to $p(X \mid S(1) = 1)$ (regression adjustment/standardization)
  - Alternative estimation strategies
    - Multiple imputation of S(1) based on X
    - Matching on X and „standard“ analysis

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ADA example: Utilizing covariates

- Case-specific whether one would be willing to make this assumption
  - Principal ignorability: untestable assumption (independence assumption „across worlds“); sensitivity analyses possible, see Ding et al. (2017)
  - If S(0) would be predictive of S(1) further analyses/assumptions would be possible → in this case as S(0) = 0 for all patients

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Criticisms

- Complication: Benefit-risk analyses for principal strata
  - Typical analysis strategies do not clearly identify the population of patients in the principal stratum. How to perform safety analyses?
- Hernán & Scharfstein (2018)
  - “... subgroup that cannot be clinically identified ...”
- Scharfstein (2018)
  - „... Principal stratification is scientifically interesting but just too assumption-laden to be primary ...“
  - “... Lowers the level of evidence. ...”
- Also controversially discussed in the causal inference community
  - See Pearl (2011)

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Summary

- Clinically relevant questions
  - Sometimes assumptions considered too strong to answer question based on the data at hand
  - But: Incorrect (& potentially mis-leading) analyses are already performed for these questions → utilizing causal inference techniques will raise the level of discussion on the questions and possible assumptions
  - More work needed on: What are plausible assumptions (& thus analyses)?
- Due to assumptions required for identification, the principal stratum strategy might not often be part of the primary estimand
- Will often still be important to contribute to an “overall” picture of the drug’s properties

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Thank you

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