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
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
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Agenda

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

• 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 $S(1)$
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
ADA example in more detail

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

• 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

Potential outcomes
\[ T(z) \text{ – Potential survival time} \]
\[ S(z) \text{ – ADA presence post-baseline} \]
 ADA example

• In potential outcome notation: Compare $T(1)|\{S(1) = 1\}$ 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
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
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
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
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)
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
References


Thank you