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

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on behalf of the causal subteam

Oncology Estimand Working Group
DAGStat Conference 2019, München
18 March 2018
Estimands in Oncology WG

- initiated and led by Evgeny Degtyarev (Novartis) and Kaspar Rufibach (Roche), first TC Feb 2018
- main purpose: ensure common understanding and consistent definitions for key estimands in Oncology across industry
- 31 members (14 from Europe and 17 from US) representing 19 companies
- established as EFSPPI SIG for Estimands in Oncology in Nov 2018
- close collaboration with regulators from EMA, FDA, China, Taiwan and Canada
Estimands in Oncology WG
Communication plan for 2019

- whitepaper(s) and presentations at statistical and clinical conferences
- plans to further engage with Clinical community beyond ASCO
Causal-Subteam

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Overview

• 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?
  • NB: The control might be a non-biologic drug (i.e. ADAs will not form)
Clinical questions

• Cancer prevention trial
  • Do patients that develop cancer (if on investigational treatment and if on control treatment) have a different cancer severity than if given the control treatment?

• Treatment switching
  • What is the treatment effect in patients that do not switch (if on investigational and if on control treatment)?
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
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• 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)
  • Conceptual idea: Potential outcomes
    S(0) and S(1) are unaffected by treatment
  • Determine treatment effect in subset(s) (principal strata) of population defined by S(0) and S(1)

• Can classify every patient in one of these four cells (= principal strata)
  • E.g. S is tumour shrinkage < X % at Y weeks or presence of ADAs

<table>
<thead>
<tr>
<th></th>
<th>S(0) = 0</th>
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<td>S(1) = 0</td>
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<tr>
<td>S(1) = 1</td>
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• Note: One of S(0) or S(1) is observed for an individual patient the other unobserved
Principal Stratification Estimands

• By itself the principal stratum formulation does not provide a solution
  • Just a way of framing a particular problem
  • But: 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 strata requires assumptions!
  • E.g. Principal stratum membership is not observed

• Let’s illustrate with the ADA example in more detail
Consider ADA example in more detail

X – Baseline Characteristics
Z – Treatment
  Z=0 control, Z=1 treatment
S – Development of ADAs
T – Survival time

• Quantity of interest?

• Survival time distributions for patients under treatment and control that develop ADAs, if taking treatment (S(1) = 1)

• In potential outcome notation: Compare
  \[ T(1) \mid S(1) = 1 \text{ versus } T(0) \mid S(1) = 1 \]
ADA example

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ADA example

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• How to derive estimate of $P(T(0) > t \mid S(1) = 1)$?
  • Unclear whether patients on the control arm would have developed ADAs if given treatment
  • Even worse: No patient on control will develop ADAs (i.e. $S(0) = 0$ for all)
  • No one-size-fits-all solution in the Frangakis and Rubin (2002) paper
ADA example: Full Bayesian estimation

• We know that

\[ p(T(0)) = \pi \ p(T(0)| \ S(1) = 1) + (1 - \pi) \ p(T(0)| \ S(1) = 0) \]

where \( \pi = P(S(1) = 1) \) can be estimated from the treatment arm.
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• Densities (or parameters describing the densities)
  • \( p(T(0)| S(1) = 1) \) and \( p(T(0)| S(1) = 0) \) are not identified based on the data  
  \( \rightarrow \) even for „infinite“ sample size, likelihood will not contract to a single point
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    → even for „infinite“ sample size, likelihood will not contract to a single point

• For a proper prior also the posterior will be proper
  • For some parameters more information might be available for others less
    → Need to evaluate impact of „weakly-informative“ priors carefully
  • See Magnussen et al. (2018) for a related approach/application
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
  • If this is true the conditional distribution \( p(T(0) \mid S(1), X) = p(T(0) \mid X) \)
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• Estimation
  • \( p(T(0) \mid X) \) can be estimated on the control group, and averaging with respect to \( p(X \mid S(1) = 1) \) provides an estimate of \( p(T(0) \mid S(1) = 1) \) (standardization)
  • Alternative estimation strategies
    • Build a model for \( S(1) = 1 \) on the treatment arm (depending on X), and multiply impute \( S(1) \) for the control arm → Combine estimate with Rubin’s rules
    • Matching on X and „standard“ analysis
ADA example: Utilizing covariates

• Case-specific whether one would be willing to make this assumption
  • Principal ignorability is an 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) → Principal stratification overused
Summary

• Clinically relevant questions
  • Sometimes assumptions too strong to answer 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

• Due to assumptions required for identification, the principal stratum strategy might not often be part of the primary estimand

• Could still be important to contribute to an “overall” picture of the drug’s properties
References


