Causal Estimand and Principal Stratum, an Overview and Potential Applications in Oncology

Feng Liu, PhD on behalf of the Causal Subteam; Oncology Estimand Working Group
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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
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
Why Causal estimand?

• ICHE9 addendum didn’t explicitly state “causal” and “causal thinking” is made implicitly via referencing potential outcomes and adoption of the principal stratum strategy.

• Causal interpretations in oncology endpoint (Kaspar 2018)
  – Hazard ratio: depending on intercurrent events and causal thinking not clear (Kaspar 2018)
  – Average hazard ratio: Under PH or NPH assumption
  – Other endpoints (Landmark, RMST etc)
Causal-Subteam (Do we have an updated teamlist?)

- Kaspar Rufibach (Roche), lead
- Vera Beckers (Abbvie)
- Björn Bornkamp (Novartis)
- Audrey Boruvka (Roche)
- Andreas Brandt (BfARM)
- Marie-Laure Casadebaig (Celgene)
- Feng Liu (AstraZeneca)
- Yi Liu (Nektar)

- Juliane Manitz (EMD Serono)
- Emily Martin (EMD Serono)
- Devan Mehrotra (Merck)
- Alan Phillips (ICON)
- Satrajit Roychoudhury (Pfizer)
- Anja Schiel (NoMA)
- An Vandebosch (Janssen)
Agenda

• Clinical Questions
• Ideas behind Causal Estimand and Principle Stratification
• Estimation of Principal Stratum Effects
• Criticisms
• Summary
Introduction to Casual Inference

• Estimand
  – A population parameter that quantifies the effect of treatment relative to control.
  – Causally interpretable (NAS report)

• Definition of causality?
  – the process of drawing a conclusion about a causal connection based on the conditions of the occurrence of an effect.

• Causal inference: Does a relation from cause to effect exist?

• In the health sciences, many of the critical questions are causal in nature

• For example:
  – What is the efficacy of a given drug on a target population?
  – What fraction of HIV infections could have been prevented by a given treatment or policy?
Evaluation Question and Attributing Causality

What is the effect of an intervention/treatment $P$ on outcome $Y$?
Example: What is the effect of an intervention/treatment ($P$) on improvement in Overall Survival ($Y$)?

Impact of $P$ =
OS ($Y$) for a cancer patient receiving intervention vs
OS ($Y$) for the same patients in the absence of the intervention
(at the same point in time)

We observe $Y$ for cancer patients receiving intervention
But we do not observe $Y$ for the same patient with receiving intervention.

Fundamental problem: We never observe the same individual with and without intervention at the same point in time

What if under post-treatment intercurrent events?
Attributing Causality

Estimate/ mimic/find a good proxy for what would have happened to outcome Y in the absence of program P

• Compare the patients with someone who ‘looks’ exactly like him/her who was not exposed to the intervention P at the same point of time

• In other words, we must find a valid Counterfactual or Control group
Identifying Causal impact Causation is not Correlation

Association: measures difference in risk between disjoint subsets of the population determined by individual’s actual treatment value

Causation: measures difference in risk in the entire population under two treatment values

Evaluate the impact/effect of an intervention on some outcomes of interest
- By how much did X (intervention) change Y (outcome)?

Not the same as correlation!
- X and Y are related, move together in some way
Clinical Questions

• Antidrug antibodies (ADA)
  – For large molecular i.e. oncology 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 (effect in sub-population)
  – See EMA anticancer guidance (Section 7.6.5) on “Analyses based on a grouping of patients on an outcome of treatment”
    • Highlights problematic nature of naive analyses
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

• Provide 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 \(Y(1)\mid \{S(1) = 1\}\) versus \(Y(0)\mid \{S(1) = 1\}\)
  – e.g. estimate survival functions \(P(Y(1) > t \mid S(1) = 1)\) and \(P(Y(0) > t \mid S(1) = 1)\) and derive a summary measure based on those

Potential outcomes
\(Y(z)\) – Potential survival time
\(S(z)\) – ADA presence post-baseline
ADA example

• In potential outcome notation: Compare $Y(1)|\{S(1) = 1\}$ versus $Y(0)|\{S(1) = 1\}$
  – e.g. estimate survival functions $P(Y(1) > t|S(1) = 1)$ and $P(Y(0) > t|S(1) = 1)$ and derive a summary measure
• Easy to derive an estimate for $P(Y(1) > t|S(1) = 1)$: 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
  \[ p(Y(0)) = \pi \ p(Y(0)|S(1) = 1) + (1 - \pi) \ p(Y(0)|S(1) = 0) \]
  – \( \pi = P(S(1) = 1) \) can be estimated from the treatment arm

• Densities
  – \( p(Y(0)|S(1) = 1) \) and \( p(Y(0)|S(1) = 0) \) not identified based on the data
    without further (e.g. parametric) assumptions

• 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
    \( \rightarrow \) 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 $X$, $Y(0)$ and $S(1)$ are independent:
    $Y(0) \perp S(1) \mid X$
  
    • Principal ignorability, see Ding et al. 2017, Feller et al. 2017
    • Similar to assumptions used in propensity score matching analyse (Austin 2010, 2014)
  – Average treatment over population Estimand: Average treatment effect (ATE) $E[Y_i(1) - Y_i(0)]$
  – Sensitivity analysis: other unmeasured confounding covariates
  – If this is true the conditional distribution $p(Y(0) \mid S(1), X) = p(Y(0) \mid X)$
ADA example: Utilizing covariates

• Estimation (see also Bornkamp & Bermann, 2019)
  – Estimate $p(Y(0) \mid X)$ 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 $\rightarrow$ 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. ...”
### Estimands (Scharfstein 2017)

<table>
<thead>
<tr>
<th>Estimands</th>
<th>Causal thinking in Hypothesis Testing</th>
<th>Assumptions</th>
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<tbody>
<tr>
<td>Treatment Policy</td>
<td>$P[Y(1)=1] \text{ vs } P[Y(0)=1]$</td>
<td>ignore intercurrent events</td>
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<tr>
<td>Hypothetical</td>
<td>$P[Y(1,R(0))=1] \text{ vs } P[Y(0, R(0))=1]$</td>
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<tr>
<td>Composite</td>
<td>$P[U(1)=1] \text{ vs } P[U(0)=1}$</td>
<td>ITT effect on composite outcome (outcome Y and IE)</td>
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<td></td>
<td>$U \text{ conditioned on outcome Y and intercurrent events}$</td>
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<tr>
<td>Principle Stratum</td>
<td>$P[Y(1)\mid R(1)=0,R(0)=0] \text{ vs } P[Y(0)=1\mid R(1)=0,R(0)=0]$</td>
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Summary

• ICHE9 addendum added causal thinking i.e. principal stratum
• Casual thinking is nature in oncology with added complexity of intercurrent events
  – Treatment policy vs principal stratum in handling intercurrent events
  – Sometimes assumptions considered too strong to answer questions
  – utilizing causal inference techniques will raise the level of discussion on the questions and possible assumptions which leads to
  – More work needed on: What are plausible assumptions (& thus analyses)?
• Ways to estimate “average causal effect”
• Due to assumptions required for identification, the principal stratum strategy might not be part of the primary estimand
• Important to contribute to an “overall” picture of the drug’s properties
References


• Scharfstein, D. (2018) A (Constructive/Provocative) Critique of the ICH E9 Addendum, Presentation given at 11th Annual Conference on Statistical Issues in Clinical Trials Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania

• Kaspar 2018 Treatment effect quantification for time-to-event endpoints–Estimands, analysis strategies, and beyond