Estimands in the Presence of Treatment Switching

Presenter: Rui (Sammi) Tang

Co-authors: Viktoria Stalbovskaya, Juliane Manitz, Marie-Laure Casadebaig, Emily Martin, Godwin Yung, Vincent Haddad, Fei Jie, Christelle Lorenzato, Jiangxiu Zhou, Evgeny Degtyarev, Hannes Buchner

Conference: ISCB, Leuven, July 2019
Outline

- Introduction to the working group
- Treatment switching subteam
- Estimand Framework
- Example study with treatment switch
- Several estimands and analyses approaches in a setting with treatment switching
- Discussion
• 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
• 34 members (15 from Europe and 19 from US) representing 22 companies
• established as EFSPISIG for Estimands in Oncology in Nov 2018 and ASA Biopharmaceutical Section SWG in Apr 2019
• collaboration with regulators from EMA, FDA, Japan, 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
Treatment switching subteam

- Viktoriya Stalbovskaya
- Juliane Manitz
- Marie-Laure Casadebaig
- Emily Martin
- Rui (Sammi) Tang
- Godwin Yung
- Vincent Haddad
- Fei Jie
- Christelle Lorenzato
- Jiangxiu Zhou
- Evgeny Degtyarev
- Hannes Buchner
IHC E9/R1: Estimand Framework

For a given trial objective: aligning target of estimation, design, method of estimation and sensitivity analysis

Trail Objective → Estimand

- Design → Data
- Main Estimator

WHAT to estimate?

HOW to estimate?

Main Estimate

Sensitivity Estimator 1 → Sensitivity Estimate 1

Sensitivity Estimator 2 → Sensitivity Estimate 2

Sensitivity analysis (assess key assumptions)
ICH E9/R1: Component of Defining an Estimand

A Population

B Variable (Endpoint)

C Intercurrent Event(s)
- Treatment discontinuation due to adverse events
- Treatment discontinuation due to lack of efficacy
- Use of rescue medication
- Treatment switch
- Death

D Population-level Endpoint Summary

Source: Devan V. Mehrotra ASA-BIOP presentation 2018
ICH E9 addendum and oncology

Why this addendum?
- Lack of alignment of trial objectives and effect estimates.
- Addendum and many (early) publications focus on longitudinally measured endpoints, especially with missing data.

What about time-to-event (T2E) endpoints?

Anticipated impact on oncology clinical trials?
Key questions

- Key intercurrent events, endpoints, and estimands in oncology?
- How do five proposed strategies to handle intercurrent events apply to T2E endpoints?
- How can established methods in oncology, e.g. censoring schemes or treatment switching, be embedded in addendum framework?
- What estimands are targeted by «standard» analyses?
- «Missing data» often highly informative. What implicit assumptions are we making when simply censoring?
- Double-blind, multicenter study with patients randomized to receive either everolimus (n = 277) or placebo (n = 139)
- Primary endpoint – Progression-free survival defined as time from randomization until disease progression or death
Example: study RECORD-1

- Positive study with clinically meaningful improvement in PFS (HR=0.33, 95% CI: 0.25, 0.43, p-value < 0.001)

Motzer et al (2010)
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- Protocol allowed crossover from placebo to everolimus upon progression (106 out of 139 patients, 76%)
- ITT analysis of OS showed trend in OS benefit (HR=0.87, 95% CI: 0.65-1.15, p-value=0.162)

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Motzer et al (2010)
Revisiting RECORD – 1
Two different estimands for OS

<table>
<thead>
<tr>
<th>Scientific question: Does experimental drug prolongs survival…</th>
<th>… regardless of crossover</th>
<th>… had cross-over not occurred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population variable</td>
<td>Targeted population</td>
<td>Targeted population</td>
</tr>
<tr>
<td>Intercurrent event: Cross-over to Everolimus</td>
<td>Treatment Policy</td>
<td>Hypothetical</td>
</tr>
<tr>
<td>Population-level summary</td>
<td>Hazard Ratio</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>Analysis</td>
<td>Estimate HR using Cox model (Red vs Black)</td>
<td>Estimate HR from RPSFT model (Red vs Green)</td>
</tr>
<tr>
<td>Additional data collection</td>
<td>-</td>
<td>Date of crossover, information needed for the model</td>
</tr>
</tbody>
</table>

These are not different sensitivity analysis, but different estimands!
Our focus

- Treatment switching methodology embedded in estimand framework
- Endpoints of interest: overall survival and PFS2
- Intercurrent events of interest: cross-over from control to experimental therapy, start of new anti-cancer therapy
- Scientific questions of interest and description of 4 attributes of corresponding estimands
- Impact on data collection
- Sensitivity and supportive analyses
Several estimands for overall survival (not an exhaustive list)

<table>
<thead>
<tr>
<th>Estimand 1</th>
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<tbody>
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<td>Scientific question: does experimental therapy prolong</td>
</tr>
<tr>
<td>Population</td>
</tr>
<tr>
<td>Variable</td>
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<tr>
<td>Intercur. event: cross-over to experimental therapy</td>
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### Several estimands for overall survival (not an exhaustive list)

<table>
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<tr>
<th>Scientific question: does experimental therapy prolong survival regardless of crossover or new therapies</th>
<th>Estimand 1</th>
<th>Estimand 2: survival in patients who did not cross-over</th>
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<tr>
<td>Population</td>
<td>Targeted indication</td>
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<tr>
<td>Variable</td>
<td>OS</td>
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<tr>
<td>Intercur. event: cross-over to experimental therapy</td>
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<td>Exclude switchers</td>
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<td>Indicator for treatment switch</td>
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**Note:** caution to use Estimand 2: breaks down randomization and potentially biased
# Several estimands for overall survival (not an exhaustive list)

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<th>Estimand 3</th>
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**Note:**

Estimand 3: **Informative censoring**
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<th>Estimand 4</th>
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<td>... survival in patients who did not cross-over</td>
<td>... survival in patients while they remained on randomized treatment or no treatment</td>
<td>... survival had cross-over not occurred and regardless of new therapies</td>
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**Population**
- Targeted indication

**Variable**
- OS

**Intercur. event: cross-over to experimental therapy**
- Treatment Policy
- Exclude switchers
- While on treatment
- Hypothetical

**Intercur. event: switch to new anticancer therapy excl. cross-over**
- Treatment Policy
- Treatment policy
- Treatment policy
- Treatment Policy

**Population-level summary**
- Hazard ratio

**Analysis**
- Estimate HR using Cox model and reported survival times
- Estimate HR using Cox model excluding patients who switched
- Estimate HR using Cox model censoring survival time at the time of switch
- Estimate HR using RPSFT and re-calculate survival times based on time spent on experimental treatment

**Additional data collection**
- Indicator for treatment switch
- Indicator for treatment switch, verification that no additional treatment had started
- Start and stop dates on experimental therapy for patients who switched

**Note:** For each estimand, analysis approach relies on different assumptions. This is important to define and discuss those assumptions with clinicians.
A hypothetical estimand

A. Population

Targeted indication: patients defined through inclusion/exclusion criteria to reflect the target patient population for drug approval

B. Endpoint

Overall survival: time from randomization until death from any cause

C. Handling of intercurrent events

*e.g.* Crossover to experimental therapy in control arm patients: survival time will be re-calculated based on time spent on experimental therapy using RPSFT and New antineoplastic therapy with the same class of drugs as experimental arm: follow treatment policy approach and not account for it

Other approach: i.e. IPCW

D. Summary measure for the variable

*Estimate hazard ratio using reconstructed data through Cox model.*

Estimand: hazard ratio of overall survival between experimental and control therapy in the targeted patient population had the crossover not occurred
Conclusions

- Addendum aims to bring more transparency around
  - connection of trial objective to estimand and estimator,
  - bias-variance trade-off of a given estimator,
  - handling of «missing» data,
  - interpretation of trial results and added value of drugs.

- More dialogues anticipated between all stakeholders ensuring key questions understood and addressed in study design and study conduct (e.g. data collection).

- Reduce overall number of (unfocused) analyses.

- Addendum has potential to change the way we design and analyze trials.

- Leadership opportunity for statisticians that are able to connect clinical to statistical questions.

- Streamline planned sensitivity/supplemental analysis and reduce overall number of (unfocused) analyses.
Current status and future outlook

- Preparation of the position paper with the estimands, strategies for handling intercurrent events, recommendations on data collection
- Active engagement within the industry, with regulators and payers
- Influence and feedback to the agency guideline to fit for oncology estimand framework
- Raise awareness of the estimands framework with the wider audience
Thank you!