Estimands in clinical trials with treatment switching

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Treatment switching is a reality and should accounted for

- Cross over maybe allowed for ethical reasons and/or practical considerations (can enhance trial participation), may be desirable and or undesirable, and may occur before any action can be taken by the monitoring committee.

- The reality of varying access to innovative treatment across study centers and countries presents additional challenges as access:
  - to subsequent treatments (including approved investigational drug in later lines), and
  - diagnostic tests and
  - standard of care may be different-

  → external validity of the trial in a specific decision context maybe be questionable

- Treatment switching has a non-negligible impact on decision making (in Germany led to an assignment of lower evidence levels\(^1\) and in NICE UK over 50% of technology appraisal were affected by treatment switching\(^2\))

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1) Isabary et al, Value in Health 21 (2018), 698-706
Indeed, standard of care across countries may be different

Patients in only nine countries have access to more than half of recently launched global cancer medicines
Treatment switching is not just limited to one scenario...

<table>
<thead>
<tr>
<th>Description of Treatment Switching</th>
<th>Type of Treatment Switching</th>
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</thead>
<tbody>
<tr>
<td>From control arm to investigational arm</td>
<td>Cross-over</td>
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<tr>
<td>From control arm to same drug class as investigational arm</td>
<td>Treatment Switching, can be analyzed using cross-over methods</td>
</tr>
<tr>
<td>From control or investigational arm to drug (class) of interest</td>
<td>Treatment Switching</td>
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</table>
A stylized example of a randomized clinical trial in Oncology with primary and final overall survival analysis

Randomized trial

- Investigational
- Control

Primary analysis
- Intermediate endpoint/or interim OS

Further follow-up

- Final OS analysis

Survival time

- Difference in intermediate outcome attributable to investigational drug
- OS difference attributable to investigational drug (followed by subsequent therapy)

Any other therapy (maybe considered standard of care (SOC) in particular country and study centre)
**A Treatment switching scenario 1: Cross over**

Randomized trial

- **Investigational**
- **Control**

Primary analysis
- Intermediate endpoint/or interim OS

Further follow-up
- Final OS analysis

- Investigational drug
- Any other therapy (maybe considered standard of care (SOC) in particular country and study centre)

**Survival time**

- Difference in intermediate outcome *attributable* to investigational drug
- OS difference *not clearly attributable* to investigational drug only
Treatment switching scenario 2: from control arm to same drug class as of investigational arm

Randomized trial

- Investigational
- Control

Primary analysis
- Intermediate endpoint/or
- interim OS

Further follow-up
- Final OS analysis

Survival time

Difference in intermediate outcome **attributable** to investigational drug

OS difference **not clearly attributable** to investigational drug only
Treatment switching scenario 3: from control arm to drug class of interest

Randomized trial

- Investigational
- Control

Primary analysis
- Intermediate endpoint/or interim OS

Further follow-up

- Final OS analysis

Survival time

Difference in intermediate outcome **attributable** to investigational drug

OS difference **not clearly attributable** to investigational drug **only**

- Investigational drug
- Compound from the same drug class as investigational drug
- Compound from a drug class of interest
- Any other therapy (maybe considered standard of care (SOC) in particular country and study centre)
A more realistic scenario is a mix of treatment switching scenarios: what are we actually measuring?

Randomized trial

- Investigational
- Control

Primary analysis
Intermediate endpoint/or interim OS

Further follow-up

- Final OS analysis

Randomize

- Investigational drug
- Compound from the same drug class as investigational drug
- Compound from a drug class of interest
- Any other therapy (maybe considered standard of care (SOC) in particular country and study centre)

Survival time

- Difference in intermediate outcome attributable to investigational drug
- OS difference not clearly attributable to investigational drug only
What are the key questions?

• The traditional approach ignores treatment switching and rest on the following assumptions:
  ✓ Subsequent therapy reflect clinical practice (including investigational drug in later line) in particular decision context
  ✓ Patients receiving subsequent treatments (from same class as investigational drug and drug class of interest) and dose intensity as expected (as SOC) between investigational and control arm

• If these assumptions do not hold, we may consider to estimate the OS benefit that is attributable to the investigational drug

• The estimand framework provides a coherent framework to make the arising issues of treatment switching explicit and offers a systematic and transparent approach for assessment
Now let us switch to the different presenter ...
The JAVELIN Lung 200 trial
• randomized
• open-label
• phase III study
→ did not meet its primary endpoint of significantly improving OS with avelumab vs docetaxel in patients with PD-L1+
NSCLC

• Subsequent IO treatments with similar MoA were approved during trial conduct and changed the respective
treatment landscape for lung cancer

• A large proportion of patients in the chemotherapy arm (docetaxel arm, 26.4%) crossed over to immune
checkpoint inhibitors (like nivolumab, pembrolizumab, etc.) outside the study

Furthermore, the approval status of new drugs within a rapidly changing treatment landscape vary across
countries

➢ The estimand framework structures the discussion about intercurrent events (here start of new therapy) and
allows granular considerations with regard to the type of therapy

Open-label studies have the risk that patients stop randomized treatment after randomization in the control arm and seek the opportunity to receive an investigational therapy in another clinical trial, possibly even from the same class as the investigational drug in the previous trial (similar to scenario 2).

Example:

Checkmate-37, comparing Nivolumab vs chemotherapy where 20% of the patients from the control arm withdrew consent immediately after they learned that they were randomized into the control arm

• Switching to products with a similar mode of action as the investigational product is considered in certain situations - but careful definition is necessary

• In immunoncology (IO), for example, the therapy could be either any IO therapy or only specific checkpoint inhibitors

➢ The estimand frameworks helps to anticipated those intercurrent events in advance. Defining different estimands and/or different estimators can in certain cases provide a fruitful solution

Further interesting examples

Example 1:

The placebo-controlled GRID trial with a high rate of crossover of placebo patients to regorafenib (85%) at progression were crossover was allowed per protocol

⇒ At primary analysis (ITT), it was shown that regorafenib improved PFS but not OS


Example 2:

The GLARIUS trial which compared standard temozolomide (TMZ) versus bevacizumab plus irinotecan (BEV+IRI) in patients with newly diagnosed glioblastoma

• Crossover to BEV+IRI therapy was given to 81.8% of all patients who received any sort of second-line therapy in the TMZ arm, affecting OS

⇒ Within such settings (similar to scenario 1) it can even happen that, on average, patients in the control arm have a similar exposure to the investigational treatment as the patients in the investigational arm

# Estimands in clinical trials with treatment switching

## Objective

## Estimand

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<th>Population</th>
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<td>Variable / Endpoint</td>
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<tr>
<td>Treatment condition of interest</td>
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## Handling of intercurrent events (IEs)

- IE: Start of subsequent therapy at any time
- IE: Crossover to investigational drug at any time
- IE: Crossover to investigational drug at disease-related time point

## Population - level Summary
# Estimands in clinical trials with treatment switching

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<thead>
<tr>
<th>OBJECTIVE</th>
<th>Evaluate OS benefit assuming subsequent therapies represent clinical practice</th>
<th>Evaluate OS benefit adjusted for treatment switching</th>
<th>Evaluate OS benefit adjusted for treatment crossover</th>
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<td>Treatment condition of interest</td>
<td>Sequence of investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapies (including investigational drug)</td>
<td>Investigational drug vs control (if there were no subsequent therapies)</td>
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<td>Population - level Summary</td>
<td>Kaplan – Meier estimates; Hazard ratio (HR) with confidence interval (CI)</td>
<td>Adjusted HR and CI from IPCW – weighted Cox model; weighted KM estimates</td>
<td>HR from RSPFT model using adjusted survival times; bootstrapped CI; KM estimates using adjusted survival times; IPCW methods could also be used</td>
<td>HR from two – stage method using reconstructed survival; modified KM estimates using reconstructed survival times; IPCW and RPSFT methods could be used</td>
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**Treatment policy**

- Defined through appropriate I/E criteria to reflect the target patient population for approval

**Hypothetical**

- Overall survival: Time from randomization to death

- Sequence of investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapies (including investigational drug)

- Investigational drug vs control (if there were no subsequent therapies)

- Sequence of investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapy (excluding investigational drug)

- Sequence of investigational drug + any subsequent therapies vs. sequence of control + any subsequent therapy (excluding investigational drug)

- Treatment policy

- Hypothetical

- Hypothetical

- Hypothetical

- Hypothetical

- Kaplan – Meier estimates; Hazard ratio (HR) with confidence interval (CI)

- Adjusted HR and CI from IPCW – weighted Cox model; weighted KM estimates

- HR from RSPFT model using adjusted survival times; bootstrapped CI; KM estimates using adjusted survival times; IPCW methods could also be used

- HR from two – stage method using reconstructed survival; modified KM estimates using reconstructed survival times; IPCW and RPSFT methods could be used

29.06.2020
Conclusions & Summary

• Treatment switching is a reality and should accounted for!
• The estimand framework provides a coherent framework to make the issues of treatment switching explicit and offers a systematic and transparent approach for assessment
• This talk focused on OS but estimands for PROs including data collection beyond progression are currently heavily debated
• Think about possible scenarios during the planning phase of a trial! Do you expect the treatment landscape to change during your trial? Look into the examples!! Many things can happen!
• There are treatment switching methods which can be applied if the necessary data is collected in the eCRF. However, they do rely on assumptions!

• Different treatment switching methods can answer different scientific questions!!

• What is better? If we do strategic country selection or if we apply methods to account for treatment switching?
Some of the content of this presentation was developed within the **European special interest group “Estimands in oncology”**, which is sponsored by PSI and EFSPI and ASA scientific working group of the ASA biopharmaceutical section.

There is also a paper submitted with the title:

**Estimands for Overall Survival in Clinical Trials with Treatment Switching**

Many thanks to everybody within the treatment switching subteam:

Juliane Manitz (EMD Serono), Natalia Kan-Dobrosky (PPD), **Hannes Buchner (Staburo GmbH)**, Marie-Laure Casadebaig (Celgene), Evgeny Degtyarev (Novartis), Jyotirmoy Dey (AbbVie), Vincent Haddad (AstraZeneca), Fei Jie (Astellas Pharma Global Development), Emily Martin (EMD Serono), Mindy Mo (Amgen), Kaspar Rufibach (F. Hoffmann-La Roche Ltd), Yue Shentu (Merck Sharp & Dohme), Viktoriya Stalbovskaya (Merus), Rui Tang (Servier Pharmaceuticals), Godwin Yung (Takeda Pharmaceuticals), Jiangxiu Zhou (GSK)