Applying the Estimand and Target Trial frameworks to external control analyses using observational data: a case study in the solid tumor setting

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Disclosure: this presentation reflects the views of the authors and not necessarily those of Hoffman-La Roche and Flatiron Health
Randomized Clinical Trials (RCTs) are the gold standard to answer causal questions about efficacy and safety of health-related interventions.

When RCTs are not feasible, high quality Real-World Data (RWD) could be considered to answer causal questions  

- At the cost of introducing further assumptions.
- Require transparency on the observational study design that emulates the target trial.

One important application in pharmacoepidemiology is the use of RWD to generate external control arms for estimating comparative treatment effect. There are several efforts to replicate trial control arms using RWD.

**Case study:** Applying the Estimand and Target Trial frameworks to replicate trial control arms from pivotal trials in non-small cell lung cancer (NSCLC) first-line setting using RWD

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1 ESMO debate session by Prof. S. Peters at ESMO Virtual Plenary April 2021; 2 Hernan MA, Robins JM. American Journal of Epidemiology; 183(8) 2016; 3 ICH E9 (R1) addendum
What’s the scientific question?

What’s the estimand of the target trial?

Set up the target randomized trial that cannot be performed

How to emulate the target trial to address the estimand?

Study design

Bring transparency on the assumptions made

Estimand & Target trial frameworks combined
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What’s the scientific question?

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Study design

Bring transparency on the assumptions made
Case study: scientific question

- **Scientific question:** Is there a difference in overall survival (OS) between patients with metastatic NSCLC\(^1\) receiving front-line platinum-based chemotherapy in pivotal trials vs patients with metastatic NSCLC who received front-line platinum-based chemotherapy as part of routine care?

Is this question clear enough to leave no ambiguity about the estimand?

\(^1\)NSCLC is the most common type of lung cancer. Metastatic NSCLC refers to later stages of the cancer where it has spread to distant parts of the body.
How to emulate the target trial to address the estimand?

- Study design
  - Bring transparency on the assumptions made

Step 3
- Set up the target randomized trial that cannot be performed

Step 4
- How to emulate the target trial to address the estimand?

What's the scientific question?

What's the estimand of the target trial?
“Is there a difference in overall survival (OS) between patients with metastatic NSCLC receiving front-line platinum-based chemotherapy in pivotal trials vs patients with metastatic NSCLC who received front-line platinum-based chemotherapy as part of routine care, regardless of whether a patient received another therapy?”

**Assumption:** subsequent treatments reflect routine clinical practice for both clinical trial and observational arms

**Risk:** differences in subsequent therapies across treatment settings may introduce complexities in estimating causal treatment effects for long-term outcomes such as OS and ultimately complicate interpretation.
“Is there a difference in overall survival (OS) between patients with metastatic NSCLC receiving front-line platinum-based chemotherapy in pivotal trials vs patients with metastatic NSCLC who received front-line platinum-based chemotherapy as part of routine care, had patients not received a subsequent therapy?”.
Metastatic squamous and non-squamous NSCLC patients, 18 years of age or older, with ECOG PS 0,1 and with adequate hematological and end-organ function.

Trial control arm and comparator observational arm (will) receive platinum-based chemotherapies. The “experimental group” receives care according to the trial protocol, whereas the “comparator” group receives care according to real-world practice.

Overall Survival

Receipt of a subsequent treatment; Strategy to handle IE: hypothetical strategy

Hazard ratio (HR) with confidence interval (CI); Kaplan-Meier estimator
What’s the scientific question?

Step 1

What’s the estimand of the target trial?

Step 2

Set up the target randomized trial that cannot be performed

Step 3

How to emulate the target trial to address the estimand?

Step 4

Study design

Bring transparency on the assumptions made

Estimand & Target trial frameworks combined
## Assumptions to emulate the target trial

<table>
<thead>
<tr>
<th>EF/TTF Attributes</th>
<th>Target trial</th>
<th>Emulation of the target trial</th>
<th>Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target population/Eligibility criteria</td>
<td>Metastatic squamous and non-squamous NSCLC patients, 18 years of age or older, with ECOG PS 0,1 and with adequate hematological and end-organ function.</td>
<td>Same as the target trial for the RCT arm, with some assumptions for the OC arm.</td>
<td>Observational data does not perfectly emulate the trial I/E criteria. We attempt to define the study cohort that best approximates the target population by including additional rules.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>● Time window for the eligibility assessment (ECOG PS, lab values, biomarker)</td>
</tr>
</tbody>
</table>
Key methodological considerations

Assignment strategy

- **Analytical strategy:**
  IPTW-ATT

- **Measured confounding variables:** age group, gender, race, metastatic tumor type, time from initial diagnosis to index date, smoking history, histology, treatment type.
Key methodological considerations

Assignment strategy

- **Analytical strategy:** IPTW-ATT

- **Measured confounding variables:** age group, gender, race, metastatic tumor type, time from initial diagnosis to index date, smoking history, histology, treatment type.

Follow-up period

- **Assumptions:**
  - Time from assignment to start of therapy is short in the RWD
  - Disease with relatively no rapid course in first-line

C, baseline confounder; E, exposure; Y, Outcome

\[
\begin{align*}
T_0 &= E=A & \text{(pooled) Trial Control arms} \\
E &= A & \text{Observational comparator arm}
\end{align*}
\]

Unknown

E, eligibility; A, treatment assignment; T0, index date; D1C1, dose 1 cycle 1
Key methodological considerations

Assignment strategy

- **Analytical strategy:** IPTW-ATT
- **Measured confounding variables:** age group, gender, race, metastatic tumor type, time from initial diagnosis to index date, smoking history, histology, treatment type.

Follow-up period

- **Assumptions:**
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Intercurrent events

- **Analytical strategy:** IPCW(t)
- **Measured confounding variables:** age group, histology/treatment, progression after treatment initiation
Key methodological considerations

- Good alignment between progression in the real world and in clinical trials [Griffith et al. 2019]
- Progression is not an exact proxy of treatment switch

Positivity assumption => there are both switchers and non-switcher at every level of the confounder (including time-varying confounders)

Intercurrent events

- **Analytical strategy:** IPCW
- **Measured confounding variables:** age group, histology/treatment, progression after treatment initiation
Baseline characteristics

- Patients enrolled in the trials were on average younger, more frequently were males, diagnosed as de novo stage IV and with squamous histology compared to patients in the real world.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories</th>
<th>Pooled_trial control arms N=849</th>
<th>Observational control arm N=3340</th>
<th>SMD Pre-IPTW</th>
<th>SMD Post-IPTW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (years), n(%)</td>
<td>&lt; 65</td>
<td>435 (51.2)</td>
<td>1222 (36.6)</td>
<td>0.42</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>≥65 and &lt;75</td>
<td>322 (37.9)</td>
<td>1268 (38.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥75</td>
<td>92 (10.8)</td>
<td>850 (25.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, n(%)</td>
<td>Female</td>
<td>248 (29.2)</td>
<td>1457 (43.6)</td>
<td>0.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Race, n(%)</td>
<td>Asian</td>
<td>105 (12.4)</td>
<td>46 (1.4)</td>
<td>0.75</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>45 (5.3)</td>
<td>921 (27.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>699 (82.3)</td>
<td>2373 (71.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG-PS, n(%)</td>
<td>0</td>
<td>314 (37.0)</td>
<td>714 (21.4)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>532 (62.7)</td>
<td>1179 (35.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>2 (0.2)</td>
<td>1447 (43.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic diagnosis, n(%)</td>
<td>De novo Stage IV</td>
<td>706 (83.2)</td>
<td>2118 (63.4)</td>
<td>0.46</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Recurrent disease</td>
<td>143 (16.8)</td>
<td>1221 (36.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking history, n(%)</td>
<td>No</td>
<td>69 (8.1)</td>
<td>257 (7.7)</td>
<td>0.02</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>780 (91.9)</td>
<td>3070 (91.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>0 (0.0)</td>
<td>13 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology, n(%)</td>
<td>Non-squamous</td>
<td>509 (60.0)</td>
<td>2278 (68.2)</td>
<td>0.17</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Squamous</td>
<td>340 (40.0)</td>
<td>1062 (31.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from initial diagnosis to index date (months), (median [IQR])</td>
<td>1.41 [0.92, 2.89]</td>
<td>1.25 [0.79, 2.27]</td>
<td>0.15</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Treatment, n(%)</td>
<td>Carboplatin+Paclitaxel</td>
<td>568 (66.9)</td>
<td>1877 (56.2)</td>
<td>0.22</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>281 (33.1)</td>
<td>1463 (43.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ECOG-PS variable was not included in the propensity score model because of the high proportion of missing ECOG-PS. Developing an imputation model to differentiate score 0 vs 1 was considered out of scope for the goal of this presentation.
Scientific question: Would there be a difference in overall survival (OS) between patients with metastatic NSCLC receiving front-line chemotherapy vs patients with metastatic NSCLC who received front-line chemotherapy as part of routine care, had patients not received a subsequent therapy?

Estimation method: Weighted Cox regression model (PH), weighted Kaplan-Meier curves
Weights*: IPTW-ATT*IPCW(t)
Accounting for censoring confounding variables

**Primary analysis**

Hypothetical strategy
IPTW-ATT*IPCW(t)

IPCW prevents from selection bias introduced by artificial censoring

**Sensitivity analysis**

Hypothetical strategy
IPTW-ATT without IPCW(t)

**Assumption (unbiased estimator):** Switcher and non-switchers have the same prognosis (i.e. no confounders)
Supplementary analysis - different strategies for IE

**Primary analysis**

IPTW-ATT*IPCW(t)  
Hypothetical strategy

Treatment switch (at 6 months):  
24% CT  
31% OC

HRw = 0.94 (95% CI: [0.77, 1.13])

**Supplementary analysis**

IPTW-ATT  
Treatment policy strategy

Wider CI

HRw = 0.92 (95% CI: [0.81, 1.05])
Study limitations

- Limited capture of potential confounders in the observational arm (e.g. comorbidities, sites of metastasis, and completeness of ECOG) - Assumption of IPTW and IPCW: no unmeasured confounding (at baseline and at time of switch)

- We have pooled together different IMpower trials
  - Added trial indicator in the PS model: treatment x histology

- Patients in IMpower trials were global while patients in the observational arm were from the United States only
The estimand framework is increasingly used by regulators but also within the clinical teams.
- Analysing RWD using the same framework as RCT avoids unneeded silos
  - Common terminology
  - Develop common analytical approaches

The combined EF/TTF brings even more clarity on the study design of the “target trial”.
- It brings transparency on the assumptions needed to emulate the target trial
- Transparent description of potential limitations of the RWD source chosen (e.g. data quality)
- Highlight the importance of variables not previously collected in the real world (e.g. intercurrent events)

This requires a new mindset:
- Become familiar with the strategies to address intercurrent events
- As per ICH E9 addendum, think carefully on what constitutes sensitivity analyses vs supplementary analyses for the key estimand also in observational research
Thank you