Electronic Health Records used to derive Control Arms for Single-Arm oncology trials: Proof of concept using RCT’s in lung cancer

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Disclaimer

• I'll present this work on behalf of those who actually conducted this study
• I might not be able to answer some questions, I'll do my very best
• EC instead of SC
Content

- The RCT as a gold standard for the study of causation
- External controls for lung cancer trials using EHR
  - Background
  - Process
  - Results
  - Conclusions and next steps
The Randomized Controlled Trial as a Gold Standard for the study of causation
Causal Effects of Treatment A

- Counterfactuals and observed outcomes. Be:
  - $Y$ the observed outcome under treatment A ($A = 0, 1$)
  - $Y_{a=0}$ the potential outcome had $A = 0$
  - $Y_{a=1}$ the potential outcome had $A = 1$

The **individual causal effect** : $ICE = Y_{a=1} - Y_{a=0}$

The **population causal effect** : $PCE = E[Y_{a=1}] - E[Y_{a=0}]$

- Causation and Correlation
  $E[Y_{a=1}] - E[Y_{a=0}] \neq E[Y|A=1] - E[Y|A=0]$  

*Fundamental problem: Estimate $PCE$ when only one counterfactual is observed*
Causal Effects and RCT

• Under which conditions is \( E[Y_{a=1}] - E[Y_{a=0}] = E[Y | A=1] - E[Y | A=0] \)?
  - Exchangeability: \( Y_a \perp A \)
  - Consistency: \( Y_a = Y \) when a subject received treatment \( A = a \)
  - Positivity: \( f_{A|L}(a | l) > 0 \) if \( f_L(l) \neq 0 \) (with confounding factors \( L \))

• Under ideal RCT conditions (i.e. full compliance, no loss to-follow-up, blind assignment)
  - \( E[Y | A=1] = E[Y_a | A=1] \) a for given \( a \)
    - \( E[Y_a | A=0] \)
    - \( E[Y_a] \)

\( E[Y_a] \perp A \ \forall \ a \ (0, 1) \)

\( \therefore \) Equation above holds
Conditional exchangeability

- Same as above but
  \[ E[Y_a] \perp A \mid L \]
  
  where \( L \) is a vector of covariates
  \[ E[Y_{a=1}] - E[Y_{a=0}] \mid L = E[Y \mid A=1] - E[Y \mid A=0] \mid L \]

- Example:
  - The Propensity Scores Theorem:
    - Be treatment A with values 0 and 1
    - The propensity of “choosing” treatment given covariates \( L \):
      \[ PS(L) = P(A=a \mid L) \]
      
      \[ \text{If} \ Y_a \perp A \mid L \quad (\text{Conditional Independence Assumption}) \]
      
      \[ \text{then} \ Y_a \perp A \mid PS(L) \quad (\text{PST}) \]
External Controls for Lung Cancer RCTs using EHR: Background
Background

- Accelerated or breakthrough regulatory approval based on single-arm trials often
  - standard-of-care control arm is not included, challenges in interpretation of efficacy
- External controls (EC) derived from electronic health record (EHR) databases may provide an additional context for interpretation
- Curated EHR datasets are now large enough, with sufficient clinical detail, to create contemporaneous EC groups
- The Flatiron Health database is a longitudinal, demographically and geographically diverse database derived from EHR data
  - 260 community-based cancer treatment clinics and 3 academic networks, > 2 million active cancer patients in the US
  - High quality mortality data for lung cancer benchmarked against the US National Death Index
Background

- Efforts towards EC
Objective

- To assess how closely results from RCTs on aNSCLC could be replicated by substituting EHR-based EC groups as the comparator
External Controls for Lung Cancer RCTs using EHR: Cohorts creation and Analysis
Trials selection

- Study on all Roche-sponsored aNSCLC RCT meeting the following:
  
  a) First patient enrolled on or after January 1, 2011
  b) mOS attained, findings presented in a journal or at a congress, by March 31, 2018
  c) including at least one US study site
  d) in the case of a biomarker-defined study population, availability of the biomarker within the curated EHR dataset
Retrieve patient level data and verify trial results

- Verify RCT results published in public forums
  - BL and demographics (Table 1)
  - Main results

**OS results for IMpower150 presented at ESMO**

- Early OS data demonstrate promising OS benefit with Arm B vs Arm C treatment regimens despite lack of data maturity

**Use case example – IMpower150 trial**

Phase 3 RCT looking at carboplatin + paclitaxel + bevacizumab vs or without atezolizumab (PD-L1 inhibitor) in frontline, non-squamous aNSCLC
Review trial protocol and identify criteria to apply

• Done cross-functionally with the study team

• Go through the I/E criteria one by one, flagging those criteria which can be applied to the EC cohort
  • Not everything will be able to be applied
    • e.g. life expectancy, comorbidities, other medications, pregnancy, etc..
  • For transparency, those criteria that are unable to be applied should be called out

• We found it especially beneficial to sit down with clinical scientists to review certain criteria and decide how best to apply to Flatiron
  • Often some “translation” needs to occur between protocol and Flatiron (e.g. staging)
Build EC cohort

• Select patients from the EHR cohort that received standard-of-care treatment as in the trial

• Apply RCT I/E criteria available in the EHR to select EHR-based controls comparable in terms of demographic and clinical characteristics with RCT patients
  – Attrition rates displayed at each step
    • Alternatively, make each criteria a flag in your dataset so that you can easily turn them on/off in different orders
  – Some criteria will be straightforward
    • Therapy of interest, Histology, Age
  – For others (ECOG and lab values), we’ve developed some business rules to alleviate issues like high levels of missingness
Data Analysis

• **Primary endpoint:** time from randomization or treatment initiation (EHR) to death (OS)

• **Statistical Analysis:**
  - Proportional hazards cox model used to estimate treatment effects (HR) comparing the experimental trial arms with EC
  - PS obtained: Probability of being in the trial treatment arm rather than in the EC given \( L \)
    - \( L = \) age, gender, race, smoking history, histology, disease stage at initial diagnosis, time from initial diagnosis to either the start of treatment (EHR data) or randomization (trial data)
    - \( L \) derived from discussions with subject matter experts
Data Analysis

• **PS Methods applied:**
  - PS stratification
  - IPTW (ATE, ATT)
  - Cox PH adjusting directly for \( L \)
  - Weights stabilization: trimming/truncation

• Sensitivity Analysis
Results
Trial selection

- From 217 RCT (8 drugs) to 9 eligible RCT
- 11 experimental arms
Building EC cohorts

Initial EC EHR group size before restriction (same treatment line of therapy as trial control arm)

Flatiron aNSCLC EHR
N=48,856

NCT02008227
N=1397 D
(atezolizumab)
NCT01903993
N=1397 D
(atezolizumab)
NCT02366143
N=1606
(atezolizumab)
1L B or C or P

NCT01351415
N=3063
(bevacizumab)
2L D/PE/E

NCT01493843
N=1606 B+C+P
N=6475 C+P
(atezolizumab)
NCT01519804
N=6506
1L PLT+

NCT01496742
N=1609 (B+
PLT)/5391

Apply Trial Inclusion/Exclusion Criteria
Histology/ECOG/Labs/Smoking History/Disease Stage/Age/Prior treatment/washout period

Final Group Size

NCT02008227
N=547
NCT01903993
N=496
NCT02366143
N=602
NCT01351415
N=381
NCT01493843
N=1,196 (SCC)
862(NSCC)
NCT01519804
N=1,908
NCT01496742
N=930 & 3200
NCT01366131
N=1,908
N=963

B=bevacizumab  PE=pemetrexed
C=carboplatin  PLT=platinum
D=docetaxel
P=paclitaxel
NSCC=non squamous cell carcinoma
SCC=squamous cell carcinoma
Trial Results

- Treatment effect estimates

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Group Comparison</th>
<th>N</th>
<th>Events</th>
<th>N</th>
<th>Events</th>
<th>RCT HR (95% CI)</th>
<th>EC adjusted HR (95% CI)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1] NCT02008227</td>
<td></td>
<td>425</td>
<td>271</td>
<td>425</td>
<td>298</td>
<td>0.73 (0.62, 0.86)</td>
<td>0.71 (0.59, 0.84)</td>
<td>0.028 (-0.132, 0.188)</td>
</tr>
<tr>
<td>[2] NCT01903993</td>
<td></td>
<td>144</td>
<td>78</td>
<td>143</td>
<td>95</td>
<td>0.72 (0.54, 0.98)</td>
<td>0.66 (0.50, 0.88)</td>
<td>0.087 (-0.176, 0.350)</td>
</tr>
<tr>
<td>[3] NCT02366143</td>
<td></td>
<td>356</td>
<td>144</td>
<td>336</td>
<td>166</td>
<td>0.77 (0.61, 0.96)</td>
<td>0.75 (0.59, 0.94)</td>
<td>0.026 (-0.179, 0.231)</td>
</tr>
<tr>
<td>[4] NCT01351415</td>
<td></td>
<td>245</td>
<td>194</td>
<td>240</td>
<td>193</td>
<td>0.88 (0.74, 1.04)</td>
<td>0.89 (0.75, 1.05)</td>
<td>-0.011 (-0.202, 0.179)</td>
</tr>
<tr>
<td>[5] NCT01493843:</td>
<td>Arm A vs. B</td>
<td>126</td>
<td>79</td>
<td>125</td>
<td>60</td>
<td>1.03 (0.75, 1.41)</td>
<td>0.95 (0.68, 1.33)</td>
<td>0.081 (-0.175, 0.337)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>79</td>
<td>59</td>
<td>79</td>
<td>43</td>
<td>1.04 (0.72, 1.50)</td>
<td>1.07 (0.78, 1.49)</td>
<td>-0.028 (-0.319, 0.262)</td>
</tr>
<tr>
<td>[7] NCT01493843:</td>
<td>Arm E vs. F</td>
<td>62</td>
<td>42</td>
<td>30</td>
<td>13</td>
<td>1.27 (0.75, 2.15)</td>
<td>1.32 (0.90, 1.93)</td>
<td>-0.039 (-0.389, 0.312)</td>
</tr>
<tr>
<td>[8] NCT01519804</td>
<td></td>
<td>55</td>
<td>36</td>
<td>54</td>
<td>33</td>
<td>0.89 (0.55, 1.46)</td>
<td>1.43 (0.97, 2.09)</td>
<td>-0.474 (-0.835, -0.114)</td>
</tr>
<tr>
<td>[9] NCT01496742:</td>
<td>Cohort 1</td>
<td>69</td>
<td>32</td>
<td>70</td>
<td>29</td>
<td>1.38 (0.75, 2.56)</td>
<td>1.26 (0.80, 1.97)</td>
<td>0.091 (-0.310, 0.492)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>59</td>
<td>37</td>
<td>61</td>
<td>36</td>
<td>1.15 (0.68, 2.56)</td>
<td>1.11 (0.73, 1.70)</td>
<td>0.035 (-0.332, 0.403)</td>
</tr>
<tr>
<td>[11] NCT01366131</td>
<td></td>
<td>52</td>
<td>24</td>
<td>52</td>
<td>18</td>
<td>1.08 (0.52, 2.21)</td>
<td>0.90 (0.53, 1.51)</td>
<td>0.182 (-0.276, 0.640)</td>
</tr>
</tbody>
</table>
Treatment effects with EC

- Trials results replicated:
  - Treatment effect estimates, except for one trial
  - Conclusions from statistical tests (H0: logHR = 0)
Conclusions

- Properly selected and adjusted control arms from high quality contemporaneous EHR data could be used to replicate results from RCT in aNSCLC
Next steps

• Fully understand why and when EC don’t work
• Methods to optimize and validate EC for single arm trials
  – Estimands & PS methods
  – Unmeasured confounding
  – rwPFS and rwOS
  – Bayesian methods
• Understand data
• Apply learnings and do the same in other tumor types (Breast, mCRC)
• Hybrid Controls (HC)
Doing now what patients need next