Assessing Strategies for Negative Control Selection

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Background

- **Negative controls** are drug exposures / outcome pairs that have no known causal relationship
- It is recommended that observational research studies should use negative controls as a bias diagnostic tool, used to calibrate the p-value to take into account random and systematic error [1]
- It is labor intensive to find negative controls manually [2] however some strategies that improve that process have been proposed (e.g. the use of Common Evidence Model (CEM))
- This poster evaluates negative control selection strategies to understand if there is an optimal strategy thus improving their use within observational research

Methods

- Adverse events of placebo/randomized clinical trials were parsed by Sherlock [3] to calculate unbiased estimates (odds ratios, OR) of true effect size for a large set of exposure-outcome pairs
- For the trial exposure-outcome pairs, evidence from CEM was summarized:
  - publish literature - count of articles suggesting adverse event association
  - product labels - 1 if mentioned on label as adverse event, else 0
  - spontaneous reports - 1 if a adverse event signal seen, else 0
- Example evidence for cyclophosphamide-constipation pair:
  - **Table 1:** for a specific trial the calculated OR is a non significant increased risk of constipation for patients on cyclophosphamide as compared to placebo
  - **Table 2:** there was publication evidence and mention on the US product label that cyclophosphamide may cause constipation

<table>
<thead>
<tr>
<th>Table 1 – Clinical Trial Calculated Odds Ratio for One Trial</th>
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</thead>
<tbody>
<tr>
<td>NCT016961125 – Tecemotide (L-144B31) in Participants With Stage III Unresectable Non-small Cell Lung Cancer Following Primary Chemo</td>
</tr>
<tr>
<td>Odds Ratio = 2.89 (p-value = 0.26)</td>
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<table>
<thead>
<tr>
<th>Table 2 – Summary Counts of Evidence from Common Evidence Model</th>
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<tbody>
<tr>
<td>Adverse Event Publication</td>
</tr>
<tr>
<td>Clinical Trial</td>
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<tr>
<td>-----------------</td>
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<tr>
<td>5</td>
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*Example publication - J Appl Pathol: 2016 – Control of Constipation in Patients Receiving CHOP or CHOP-like Chemotherapy Regimens for Non-Hodgkin’s Lymphoma
**Example Label - 605154-1-687-454-6-AW-48755-5-5f-9-ep-6-4f-6: lists constipation an adverse event in the post-marketing experience

- **Negative Control Selection Strategies** (in order of complexity):
  - **Strategy 1** – All Available Prevalent Exposure-Outcome Pairs
  - **Strategy 2** – Exclude Pairs with CEM Evidence (Exact Outcome Terms Only)
  - **Strategy 3** – Exclude Pairs with CEM Evidence (with Associated Related Outcomes)
  - **Strategy 4** – Automated Method of Pair Selection using CEM Evidence [2]
  - **Strategy 5** – Automated Method of Pair Selection using CEM Evidence [2] with Manual Curation*

  *Manual curation will be performed by two physicians independently, in progress currently

- First four strategies were evaluated on their success of removing non-negative exposure-outcome pairs from the set extracted trials, if all remaining pairs are negative it would be expected exactly 5% to have an OR with a p<0.05
- Method for estimating the empirical null distribution [1] employed on the four strategies to measure whether the distribution of effect size estimates was consistent with the null being true for all

Results

- For each strategy, we plot the exposure-outcome pairs (Figure 1-4):
  - Blue dots each represent one pair by odds ratio vs standard error
  - Red diamond example evidence (saxagliptin-influenza) that exists in all four plots
  - Grey area below the dashed line represents the traditional p-value (dots in this area are significant)
  - Orange area represents the calibrated p-value (if the orange area does not equals the grey there is error)
  - Mean / Standard Deviation (STDEV) of the estimated null distribution (log scale)

Conclusions

- Since we do not believe there is bias in these estimates, we would expect a mean = 0 and STDEV = 0 if the null (of no effect) is true for all drug-outcome pairs that remain after the selection strategy
- Example evidence in all plots is saxagliptin and influenza:
  - no publication / US product label /spontaneous reports suggesting there was a causal association
  - automated method selected as potential negative control pair

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References