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 case constipation

Table 1 – Clinical Trial Calculated Odds Ratio for One Trial
NCT00960115 - Tecemotide (L-BLP25) in Participants With Stage III Unresectable Non-small Cell Lung Cancer Following Primary Chemo
Odds Ratio = 2.99 (p-value = 0.26)

Table 2 – Summary Counts of Evidence from Common Evidence Model

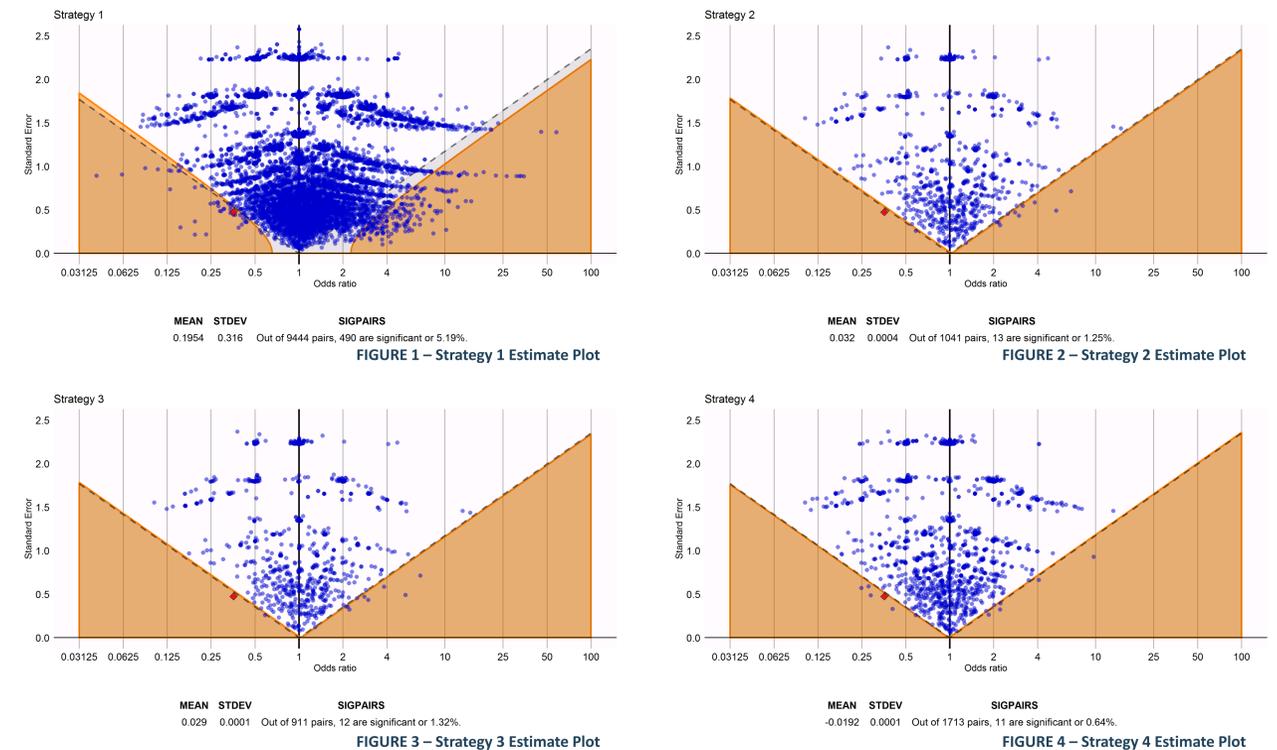| Adverse Event Publication			Adverse Event Publication (NLP)			-	-	-
Clinical Trial	Case Report	Other	Clinical Trial	Case Report	Other	US Product Labels	EU Product Labels	Spontaneous Reports
5	0	8*	0	1	1	1**	0	0
* Example publication – 28458356 - Control of Constipation in Patients Receiving CHOP or CHOP-Like Chemotherapy Regimens for Non-Hodgkin's Lymphoma								
** Example Label - 6bae5c14-9e87-4fb6-ae9c-4d875c1ecffe- 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)

MEAN STDEV   SIGPAIRS
0.1954 0.316   Out of 9444 pairs, 490 are significant or 5.19%.
FIGURE 1 – Strategy 1 Estimate Plot

MEAN STDEV   SIGPAIRS
0.032 0.0004   Out of 1041 pairs, 13 are significant or 1.25%.
FIGURE 2 – Strategy 2 Estimate Plot

MEAN STDEV   SIGPAIRS
0.029 0.0001   Out of 911 pairs, 12 are significant or 1.32%.
FIGURE 3 – Strategy 3 Estimate Plot

MEAN STDEV   SIGPAIRS
-0.0192 0.0001   Out of 1713 pairs, 11 are significant or 0.64%.
FIGURE 4 – Strategy 4 Estimate Plot

- 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

Conclusions

- Implementing Strategies 2-4 (Figures 2-4) bring the OR closer to 1 and STDEV closer to 0 suggesting the pairs left are more representative of negative controls

- Strategies 2-3 are simpler methods and reach similar resulting negative controls pairs to Strategy 4

- Strategy 4, a more complicated method however preserves more pairs than Strategies 2-3

[1] Schuemie MJ, Ryan PB, DuMouchel W, Suchard MA, Madigan D. Interpreting observational studies: why empirical calibration is needed to correct p-values. Stat Med. 2014 Jan 30;33(2):209-18. doi: 10.1002/sim.5925. Epub 2013 Jul 30. PubMed PMID: 23900808; PubMed Central PMCID: PMC4285234.
[2] Voss, E.A., et al., Accuracy of an automated knowledge base for identifying drug adverse reactions. J Biomed Inform, 2017. 66: p. 72-81.]
[3] Cepeda, M.S., V. Lobanov, and J.A. Berlin, Use of ClinicalTrials.gov to estimate condition-specific nocebo effects and other factors affecting outcomes of analgesic trials. J Pain, 2013. 14(4): p. 405-11.

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