Automated methods to generate negative controls for self-controlled cohort designs produce reliable results quickly.

**INTRO**

- The Real-World Assessment of Drug Benefits (REWARD-B) platform utilizes a self-controlled cohort design to find associations between all drugs and all conditions as a way to discover unknown benefits of existing therapies and requires negative control calibration to produce valid results.
- Self-controlled study designs produce less biased estimates than other study designs yet remain prone to systematic bias.
- Applying negative controls is an effective way to control for systematic bias.
- However, manual selection of controls can be time consuming, resource-intensive, and prone to human error.
- The purpose of this research is to compare the performance of automated selection of negative control sets versus a hand curated set.

**METHODS**

- Benefits of existing medications for incident Bipolar Disorder were examined utilizing the REWARD-B platform.
- Analyses were performed in IBM MarketScan® Commercial Database (CCAS). Incident rate ratios were calculated, and calibrated p-values were generated by estimating the systematic error distribution using four sets of negative controls: three automated and one manually curated (Table 1).

**RESULTS**

- A total of 2,592 medications were evaluated.
- The uncalibrated results using set 1 showed 15% (n=388) of medications had a statistical association with Bipolar Disorder (p<0.05), which is higher than the expected 5%, indicating bias in the study design (Figure 1); similar proportions were found in other sets.
- Results from each of the four negative control sets demonstrated strong negative bias and were similar between each of the 3 automated sets and the manually curated set (Figure 1).

**CONCLUSION**

- Empirical calibration is necessary to adjust for systematic bias that arises from the self-controlled cohort design.
- When applied to the REWARD-B platform, we demonstrated that automated procedures used to generate negative controls perform as well as manually generated negative controls, while taking only a fraction of the time to implement.
- Further research is needed to explore these findings in other disease areas and for negative control outcomes.