

# Performance of Screening Multiple Observational Databases for Active Drug Safety Surveillance

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## Abstract

**Background:** Electronic health records (EHR) and administrative claims databases offer the potential to supplement the identification of potential safety concerns of medicines post-approval.

**Objectives:** To evaluate the performance of alternative screening methods for identifying drug-condition associations across two disparate observational databases.

**Methods:** Two observational databases- a claims and an EHR- were used. 10 drugs with different indications, utilization, and safety profiles were selected as test cases, with adverse events listed on each US product label identified as potential true associations. Screening rate ratio (SRR) metrics and lower bounds (LB) of 95% confidence intervals based on retrospective cohort and self-controlled designs were examined. ROC curves were produced to examine optimal tradeoffs of sensitivity and specificity of 1448 source-metric-threshold combinations for each drug. Spontaneous data mining (SDM) on AERS was conducted using two common thresholds: MGPS EB05>2 and Evans criteria (PRR>2, n>3, 2>4).

**Results:** Across all 10 drugs, 1391 distinct labeled events were identified as potentially detectable in AERS, claims and EHR. Metrics comparing rates post-exposure to overall population performed better than within-cohort (pre-post) methods. Screening for significant associations in both sources (SRR post/overall LB>1) had 39% sensitivity and 85% specificity. Raising the threshold to LB>1.5 produced improved specificity (94%) at the expense of sensitivity (15%). AERS EB05>2 yields 8% sensitivity and 95% specificity. A composite threshold requiring detection in both sources had increased performance to thresholds based on only one source or compared to SDM. Performance of methods varied by drug, as well as the severity and rarity of the events.

**Conclusions:** Observational screening is a promising approach for detecting potential safety concerns as part of an active pharmacovigilance system. Use of multiple databases greatly improves performance in identifying true drug-condition associations.

## Conflicts of Interest

- None

## Background

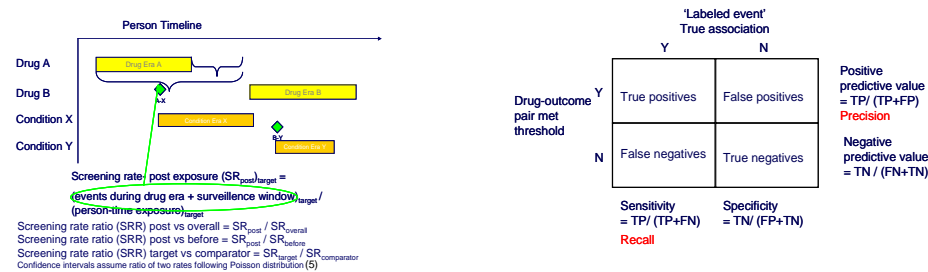
Recent calls have been made to establish a national active drug safety surveillance system that leverages observational data, including administrative claims and electronic health records, to monitor and evaluate potential safety issues of medicines(1-3). Several initiatives aim to inform efforts in this area(4). However, the development and evaluation of appropriate statistical methods for observational data have not yet been comprehensively studied to assess the impact on current pharmacovigilance practice.

## Objectives

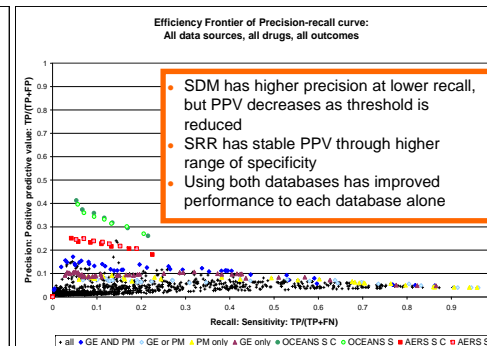
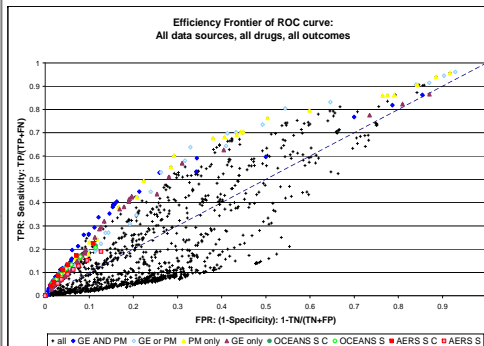
To evaluate the performance of alternative screening methods for identifying drug-condition associations across two disparate observational databases

## Methods

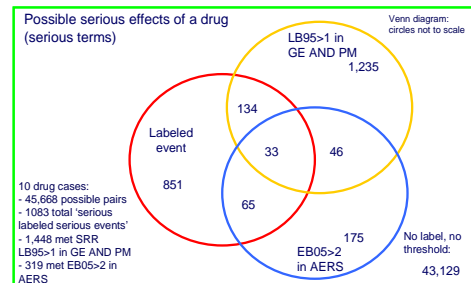
Two observational databases- PharMetrics (PM) claims database and GE Centricity (GE) electronic health record- were used. 10 drugs with different indications, utilization, and safety profiles were selected as test cases, with adverse events listed on each US product label identified as potential true associations. Screening rate ratio (SRR) metrics and lower bounds (LB) of 95% confidence intervals based on retrospective cohort and self-controlled designs were examined. Spontaneous data mining (SDM) on AERS was conducted using two common thresholds: MGPS EB05>2 and Evans criteria (PRR>2, n>3, 2>4).



## Results



Average performance across 10 drug cases, in GE AND PM								
Threshold (POST30D/OVERALL)	TP	FN	FP	TN	Sens	Spec	PPV	NPV
<b>Serious outcomes</b>								
LB95>1.5	7.4	43.9	52.2	989.6	0.14	0.95	0.12	0.96
LB95>1.25	11.8	39.5	78.7	963.1	0.23	0.92	0.13	0.96
LB95>1	16.7	34.6	127.9	913.9	0.33	0.88	0.12	0.96
<b>Non-serious outcomes</b>								
LB95>1.5	12.9	74.9	106.8	1609	0.15	0.94	0.11	0.96
LB95>1.25	22.5	65.3	182.2	1534	0.26	0.89	0.11	0.96
LB95>1	37.5	50.3	297.7	1418	0.43	0.83	0.11	0.97



## Results (cont.)

- Across all 10 drugs, 1391 distinct labeled events were identified as potentially detectable in AERS, claims and EHR
- Metrics comparing rates post-exposure to overall population performed better than within-cohort (pre-post) methods
- Screening for true associations in both sources (SRR post/overall LB>1) had 39% sensitivity and 85% specificity
- Raising the threshold to LB>1.5 produced improved specificity (94%) at the expense of sensitivity (15%)
- AERS EB05>2 yields 8% sensitivity and 95% specificity
- A composite threshold requiring detection in both sources had increased performance to thresholds based on only one source or compared to SDM
- Performance of methods varied by drug, as well as the severity and rarity of the events
- Identification using both SDM and SRR yields 137% more serious labeled events than SDM alone

## Conclusions

- Observational screening is a promising approach for detecting potential safety concerns as part of an active pharmacovigilance system
- Use of multiple databases improves performance in screening for potential drug safety issues
- Incremental gains in identifying true associations come at acceptable tradeoff with specificity
- Restriction to serious outcomes can focus attention on important events while reducing number of false positive findings
- Given its performance, screening (hypothesis generating) analyses should be tightly coupled with rapid semi-automated approaches for hypothesis strengthening
- Further research is needed to improve methods, including automated adjustment for confounding, and determine best use of data and methods to complement current practice

## References

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