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Original Research Article

Mechanism-based simulation of comparator selection in pharmacovigilance signal detection

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ABSTRACT

Background: Reference set choice can influence automated disproportionality analysis of spontaneous reporting data. Active comparators may reduce confounding by indication but can increase susceptibility to masking and reporting differences. This study examined comparator effects under different clinical and reporting conditions.
Methods: A controlled simulation separately modelled event generation, reporting, and analysis. Full-data, active-comparator, and class-exclusion reference sets were compared across nine prespecified scenarios involving confounding by indication, masking, differential reporting, and their combinations. Each scenario included 5,000 Monte Carlo replicates. The primary outcome was the pairwise difference in mean log-ROR. Sensitivity analyses examined comparator similarity, while exploratory analyses assessed masking intensity and consistency using PRR and BCPNN. A published FAERS analysis provided an illustrative external comparison.
Results: Under masking, mean RORs were 1.481, 0.759, and 1.933 for full-data, active, and class-exclusion comparators, respectively. The active versus full difference in mean log ROR was −0.670. Under combined confounding and masking, corresponding RORs were 1.543, 0.771, and 2.331, with a difference of −0.696. With confounding alone (true OR=1.0), the active comparator reduced mean ROR from 1.126 to 1.008. Findings were consistent across comparator similarity levels and with PRR and BCPNN.
Conclusions: Comparator effects depended on the underlying conditions. Active comparators reduced distortion from confounding by indication but could lower disproportionality estimates when masking occurred. Comparator selection should therefore consider the clinical and reporting factors that shape spontaneous reporting data rather than assume active comparators are always preferable.

Keywords: Pharmacovigilance, Disproportionality, Masking, Comparators, Confounding, Signal detection, Simulation

INTRODUCTION

Post marketing safety surveillance of a drug is necessary to identify adverse events not known at the time of approval of the drug by the regulatory agencies. Adverse event reports are collected and stored in the global data base VigiAccess (WHO) and national and regional data bases such as U.S. Food and Drug Administration Adverse Event Reporting System (FAERS), EudraVigilance (European database of suspected adverse drug reaction reports, Canada Vigilance Adverse Reaction Online Database, Database of Adverse Event Notifications (DAEN) in Australia etc. The presence of an adverse event report does not prove that the drug caused the effect, it shows only a temporal association or an observer's opinion or suspicion. The reports often lack many details including

dosage, medical history, concurrent medications etc. as these reports are either voluntary or are submitted by manufacturers. There might be under reporting of adverse reactions as well as over reporting due to media attention to a particular drug or its adverse effects or regulatory warnings. The reported adverse reaction might also be due to the underlying clinical condition or concomitant drugs. Another important critical limitation is the inability to make numerical comparisons or calculate the true risk or exact incidence rate of a side effect as the total number of adverse reactions occurring or total patient drug exposure numbers are unknown. The calculations also need to consider the number of years the drug has been on the market.

Researchers use these large adverse event data bases to detect potential drug side effects, medication errors and emerging safety signals that the clinical trials might not have captured. A safety signal refers to information on a new or known adverse event that is potentially caused by a medicine and that warrants further investigation.[1] As the ADR databases do not provide a conventional denominator of exposed individuals, disproportionality analysis is widely used for analysis of databases. Disproportionality analysis applies statistical algorithms such as reporting odds ratio (ROR), proportional reporting ratio (PRR) and Bayesian approaches for finding whether a specific adverse event is reported more frequently for a given drug than expected across the database.[1-4] The resulting estimate depends on the reporting reference set used for comparison (comparator) and are also affected by features of the reporting background.[5] The comparator used is therefore part of the analysis rather than a neutral background choice.[6,7]

Several comparator strategies are used for disproportionality analyses, including an unrestricted comparator (full reporting database), an active comparator (an alternative, approved drug used as a benchmark), and class-exclusion approaches. Gravel and Douros reviewed the advantages and limitations of these strategies and highlighted that these analyses require careful interpretation due to inherent observational biases. They emphasised that comparator choice should be considered in relation to the potential sources of bias in the drug–event question.[6] As the study drug and active comparator are used for similar clinical indications, an active comparator potentially reduces channelling bias by ensuring both treatment groups share similar clinical indications and baseline disease severity. This design choice minimizes confounding by indication, aligning the comparison groups more closely.[2] A study by Alkabbani and Gamble showed that active-comparator restricted disproportionality analysis can materially change signal estimates in FAERS.[8]

The same restriction may also increase the influence of masking. Masking is the false suppression or skewing of detected safety signals of a drug due to presence of dominant adverse event reports for other drugs in the same class. Masking has been described mathematically and evaluated in simulation studies.[9,10] More recent FAERS evidence suggests that masking may be particularly amplified under active-comparator designs.[11] Calendar time is also relevant to comparator selection as the magnitude and direction of stimulated or notoriety-related reporting may vary across drugs and events.[7,12-14]

Disproportionality measures in pharmacovigilance only signal statistical associations between drugs and adverse events and should not be interpreted as causal effect estimates unless the assumptions required for such an interpretation are reasonably satisfied.[15] A recent causal framework for pharmacovigilance similarly argues that confounding, selection, measurement and reporting mechanisms should be considered explicitly rather than treated as a single generic source of bias.[16]

It is well documented that comparator choice can alter disproportionality estimates. However, observational spontaneous-reporting data cannot separate the contribution of individual event-generation and reporting mechanisms.[6,7] A controlled mechanistic simulation isolates event generation and reporting mechanisms and quantify their effects on pharmacovigilance signal estimates overcoming the limitations of observational spontaneous-reporting analysis. We therefore conducted a controlled methodological simulation to evaluate how reference-set construction influences disproportionality estimates under distinct clinical and reporting mechanisms.

We used simulation to examine how confounding by indication, masking, differential stimulated reporting, and differential calendar-time reporting affect comparator-dependent change in log-ROR. The primary estimand was the change in log-ROR produced by changing the comparator under each prespecified mechanism.[6,7,9,10,12-14,16] Because comparator choice can influence whether a drug-event combination is prioritized for further safety assessment, understanding the mechanism-specific behaviour of reference sets has direct implications for pharmacovigilance signal triage.

METHODS

Study design and analytical perspective

This was a methodological simulation study conducted from January 2026 to October 2026, informed by the published pharmacovigilance literature on comparator choice, masking, stimulated reporting and causal bias. The simulation formed the primary analysis.

A formal FAERS validation analysis was not performed in the present study because no independent drug–event setting meeting all prespecified eligibility and methodological-overlap criteria had been finalized before analysis.

Causal framework

The simulation was treated as three linked stages: a latent event-generation process representing treatment assignment and event risk, a reporting process that determines which simulated events appear in the spontaneous-reporting database, and analysis of the observed reports. The prespecified mechanisms were confounding by indication, masking, differential stimulated reporting, differential calendar-time reporting, and two combined-mechanism scenarios. The causal structure defined the simulation mechanisms and their expected direction of comparator-dependent change in log-ROR. RORs were treated as disproportionality measures rather than causal effect estimates.[15,16]

Data-generating process

Each replicate contained 50,000 latent individuals, as prespecified in the pre-analysis protocol, and this population size was held constant across the primary simulation scenarios and comparator-similarity sensitivity analyses. Indication prevalence was 0.35. Drug assignment and event occurrence were generated probabilistically within this latent population, followed by a separate reporting process that determined which simulated events entered the observed reporting database. Three drug states were defined: A (study drug), B (active comparator) and O (background). Drug assignment was generated from the indication structure. The prespecified true event-generation odds ratio (OR_{true}) was set to 1.0 or 2.0, and the event model also incorporated an indication effect in confounding scenarios. A separate reporting model then determined whether each event appeared in the simulated reporting database.

For the primary confounding scenarios, the indication coefficient for A was 1.0 and that for B was 0.90. The primary reporting parameters were a baseline reporting probability of 0.10, an event-reporting coefficient of 1.20, baseline drug-specific reporting coefficients of 0.20 for A and 0.10 for B, and a masking coefficient of 2.0 for the B×event interaction. For differential stimulated reporting, coefficients of 1.60 for A and 0.50 for B were applied after calendar time 0.60. For differential calendar-time reporting, coefficients of 1.40 for A and 0.40 for B were applied as a time-varying reporting component.

Scenarios

The nine simulation scenarios are summarised in Table 1.

Table 1: Prespecified simulation scenarios and reporting mechanisms.

Scenario	OR_{true}	Mechanism	Operational definition in the simulation
S1	1.0	Null, clean reporting	No confounding or differential reporting mechanism; baseline reporting process applied uniformly.
S2	2.0	Prespecified event-generation effect, clean reporting	Prespecified event-generation effect with no confounding or differential reporting mechanism.
S3	1.0	Confounding by indication	Indication affects both drug assignment and event risk, with different indication coefficients for study drug A and comparator B.
S4	2.0	Confounding by indication	Prespecified event-generation effect combined with confounding by indication.
S5	2.0	Comparator masking	Event reporting for comparator B is increased, raising the reporting background against which study drug A is evaluated.
S6	2.0	Differential stimulated reporting	After the prespecified time point, event reporting is stimulated differently for A and B.
S7	2.0	Differential calendar-time reporting	Reporting trajectories for A and B differ continuously over the normalized calendar-time variable.
S8	2.0	Confounding + masking	Confounding by indication is combined with increased event reporting for comparator B.
S9	2.0	Confounding + differential reporting	Confounding by indication is combined with differential reporting between A and B after the prespecified time point.

OR_{true} denotes the prespecified odds ratio governing the event-generation model and is not assumed to be numerically equivalent to the observed reporting odds ratio (ROR). Clean reporting denotes the baseline reporting process without the comparator-related differential reporting mechanisms introduced in the other scenarios. The masking and differential-reporting mechanisms represent controlled simulation stress-test conditions and are not intended to represent empirically calibrated reporting parameters for a specific medicine.

Formal data-generating equations

Treatment assignment

$\eta A = -1.5 + \beta A \times I$

$\eta B = -1.5 + \beta B \times I$

$P(A \mid I) = \exp(\eta A) / [1 + \exp(\eta A) + \exp(\eta B)]$

$P(B \mid I) = \exp(\eta B) / [1 + \exp(\eta A) + \exp(\eta B)]$

$P(O \mid I) = 1 - P(A \mid I) - P(B \mid I)$

Event generation

$\text{logit}[P(Y = 1)] = -3.2 + \log(OR\text{true}) \times A + 0.8 \times C \times I$

A=1 for study-drug exposure; C is the confounding-strength parameter.

Reporting generation

$\text{Logit}[P(R = 1)] = \text{logit}(0.10) + 1.2Y + 0.2A + 0.1B + 2.0(BY)$

For differential stimulated reporting, add: $1.6 \times (A \times Y \times 1[t \geq 0.60]) + 0.5 \times (B \times Y \times 1[t \geq 0.60])$

For differential calendar-time reporting, add: $1.4(AYt) + 0.4(BYt)$

Definitions

I denote the binary indication status (1 = indication present, 0 = indication absent). βA and βB are the indication coefficients governing assignment to study drug A and active comparator B, respectively. ηA and ηB are the corresponding linear predictors for treatment assignment. A is an indicator for exposure to the study drug (1=exposed, 0=not exposed). B is an indicator for exposure to the active comparator (1=exposed, 0=not exposed). O denotes the residual background reporting state. Y denotes occurrence of the simulated event (1=event, 0=no event). R denotes whether an event is reported in the simulated spontaneous-reporting database (1=reported, 0=not reported). t denotes the normalized calendar-time variable. C denotes the confounding-strength parameter. A signal was defined as a lower 95% confidence limit for the ROR greater than 1. The event-generation model used OR_{true}=1.0 in null scenarios and OR_{true}=2.0 in positive-effect scenarios; the primary confounding setting used β=1.0 and βB=0.90.

Comparator strategies

The full-data comparator included all observed reports not involving study drug A. The active comparator included reports involving B only. The class-exclusion comparator included reports involving O, with B excluded from the reference set. In the simulation, O represents a residual background reporting state and therefore operationalises class-exclusion as a simplified reference-set abstraction. It does not implement a specific pharmacological class-exclusion algorithm or imply that all empirical class-exclusion strategies consist of the residual background after removal of an active comparator. The simulated class-exclusion strategy was used to examine how a restricted reference set could alter disproportionality estimates under the prespecified mechanisms.

Primary estimands

The primary estimands were pairwise differences in log-ROR. In this study, comparator-dependent change in log-ROR was defined operationally as the difference in log-ROR between two comparator strategies, with the direction determined by the order of the comparison.

$\Delta\text{active}-\text{full} = \log(ROR\text{active}) - \log(ROR\text{full})$

$\Delta\text{class-exclusion}-\text{full} = \log(ROR\text{class-exclusion}) - \log(ROR\text{full})$

$\Delta\text{active}-\text{class-exclusion} = \log(ROR\text{active}) - \log(ROR\text{class-exclusion})$

Mean log-ROR was used as the primary summary scale because the logarithmic transformation makes multiplicative differences in ROR additive and provides a symmetric scale for comparing comparator-dependent changes; differences between mean RORs were therefore not used as the primary contrast. A clean-reporting reference generated from the same model was retained as a secondary diagnostic for reporting-process distortion; it was not treated as a causal gold standard.

Disproportionality estimation

The primary estimator was the reporting odds ratio (ROR). The ROR was selected because it is widely used in spontaneous-reporting signal detection and has a direct 2×2 case–non-case interpretation.[1-3] The ROR was calculated from the 2 × 2 table as ROR = ad / (bc) where a, b, c and d denote the corresponding cell counts. When any cell count was zero, a continuity correction of 0.5 was added to all four cells. The standard error of the natural logarithm of the ROR was calculated as $SE[\log(ROR)] = \sqrt{(1/a + 1/b + 1/c + 1/d)}$. The 95% confidence interval was calculated on the log scale as $\log(ROR) \pm 1.96 \times SE[\log(ROR)]$ and then exponentiated to obtain the confidence limits on the ROR scale.

The proportional reporting ratio (PRR) and the Bayesian confidence propagation neural network (BCPNN) information component (IC) were not part of the prespecified primary analysis. They were later evaluated as post-freeze exploratory estimator sensitivities using the retained 2×2 cell counts and are reported separately. A

signal was defined as a lower 95% confidence limit for the ROR exceeding 1.

Monte Carlo design and performance measures

The parameters were selected to produce separable and mechanistically distinguishable event-generation and reporting processes; sensitivity analyses assessed whether the principal comparator contrast depended on these choices. Five thousand replicates were generated for each of the nine primary scenarios.

Random-number generation was made reproducible using deterministic, scenario- and replicate-specific seeds. For the primary simulation, the seed was defined as Primary simulation seed = 100000 + s × 10000 + r, where s denotes the scenario index and r the replicate number. The comparator-similarity sensitivity analyses used the deterministic seed 500000 + round (OR_{true} × 1000) + round (S × 100) + r, where S denotes the prespecified comparator-similarity level. The R random-number generator was therefore reinitialized deterministically for each replicate.

Comparator-similarity sensitivity analysis

For S3 and S4, comparator similarity was varied by changing the ratio of the indication coefficient for B to that for A. The prespecified values were 0.95, 0.90 and 0.70. Five thousand replicates were run at each level. The main sensitivity outcome was Δ active–full.

Prespecified analyses and post-simulation analysis

The prespecified empirical FAERS validation component was not conducted as a formal, independently selected case study. No independent drug–event setting satisfying all predefined eligibility, methodological-overlap and feasibility criteria was finalised before completion of the simulation without introducing post hoc case selection. Instead, a published FAERS analysis involving documented masking associated with stimulated reporting (Bai, Douros and Gravel, 2025) was examined post-simulation as an illustrative external consistency check. This illustration does not alter the primary simulation estimands or results and is presented separately in the results section.

Reproducibility

The final v5 analysis was executed in R version 4.6.1. Random-number generation used deterministic scenario- and replicate-specific seeds as described above. All nine scenarios completed the planned 5,000 replicates. The analysis code and protocol were archived before the final simulation. Comparator definitions, analysis periods, signal criteria, and simulation parameters were reported explicitly to improve transparency and reproducibility, consistent with published recommendations for reporting disproportionality analyses.[17,18]

RESULTS

All nine primary scenarios completed the planned 5,000 replicates. Prespecified simulation checks confirmed finite ROR and log-ROR estimates for the final analysis. Under clean conditions, comparator estimates were similar, with minimal signal-classification discordance (Table 2).

Under confounding, the active comparator produced a comparator-dependent change in log-ROR toward the prespecified event-generation odds ratio in the null scenario (S3). The same directional difference persisted when OR_{true}=2.0 (S4) (Tables 2 and 3).

Under masking (S5), the active comparator produced a substantially lower ROR than the full-data comparator (0.759 vs 1.481), with signal classification differing in 98.14% of replicates (Tables 2 and 4). Across masking coefficients from 0.5 to 3.0, the active-versus-full contrast remained negative and became larger as masking increased. Differential stimulated reporting and calendar-time reporting reduced the active-versus-full log-ROR by 0.099 and 0.094, respectively, without changing signal classification.

The largest comparator differences occurred when confounding and masking were combined (S8), where the active-versus-full difference in mean log-ROR was −0.696 and signal classification differed in all 5000 replicates. Under confounding plus differential reporting (S9), the corresponding difference was −0.213. The active-comparator ROR remained lower than the full-data comparator ROR at all prespecified similarity levels. In S3, Δ_active–full was −0.088, −0.114 and −0.120 at similarity coefficients of 0.70, 0.90 and 0.95. In S4, the corresponding values were −0.087, −0.113 and −0.119.

In post-freeze exploratory analyses, PRR and BCPNN produced the same qualitative comparator ordering as ROR in S5 and S8, indicating that the observed comparator dependence was not specific to the ROR.

Exploratory FAERS consistency check

As a post-simulation illustrative consistency check rather than a formal external validation, we examined a published FAERS analysis of pioglitazone and cardiovascular events. Bai, Douros and Gravel used rosiglitazone as a masking candidate and compared full-data comparator and active-comparator designs before and after cardiovascular safety concerns.[11] In the post-concern period, the relative change-in-estimate for the pioglitazone–myocardial infarction PRR after removal of the mask was 0.41 with the full-data comparator and 18.00 with the active comparator; corresponding values for cardiac failure were 0.04 and 1.03. Changes in the information component showed the same pattern.[11] These findings were directionally consistent with S5 and S8, in which the active comparator produced lower disproportionality estimates than the full-data comparator when masking was present. This was not

a formal external validation of the simulation parameters or effect sizes, but provides empirical context for the mechanism examined here.[11] The primary simulation results are summarised in Table 2. Signal defined as a lower 95% confidence limit of ROR >1. Values are the proportion of 5,000 Monte Carlo replicates meeting this criterion for each scenario/comparator. The corresponding pairwise differences in mean log-ROR are shown in Table 3.

Signal-classification discordance across comparator strategies is shown in Table 4. The comparator-similarity sensitivity results are shown in Table 5.

Table 2: Mean reporting odds ratios and signal rates across comparator strategies in the nine prespecified simulation scenarios.

Scenario	Comparator	Mean ROR	Mean log-ROR	Signal detection rate (%)
S1	Full	0.972	−0.036	1.78%
S1	Active	0.995	−0.018	2.14%
S1	Class-exclusion	0.969	−0.039	1.72%
S2	Full	1.945	0.661	100.0%
S2	Active	1.992	0.679	99.92%
S2	Class-exclusion	1.940	0.657	100.0%
S3	Full	1.126	0.115	24.80%
S3	Active	1.008	0.001	2.74%
S3	Class-exclusion	1.175	0.157	38.50%
S4	Full	2.231	0.800	100.0%
S4	Active	2.000	0.688	100.0%
S4	Class-exclusion	2.327	0.841	100.0%
S5	Full	1.481	0.388	98.14%
S5	Active	0.759	−0.281	0.00%
S5	Class-exclusion	1.933	0.654	100.0%
S6	Full	2.806	1.028	100.0%
S6	Active	2.553	0.929	100.0%
S6	Class-exclusion	2.884	1.055	100.0%
S7	Full	2.891	1.058	100.0%
S7	Active	2.643	0.964	100.0%
S7	Class-exclusion	2.967	1.083	100.0%
S8	Full	1.543	0.431	98.14%
S8	Active	0.771	−0.264	0.00%
S8	Class-exclusion	2.331	0.843	100.0%
S9	Full	3.184	1.156	100.0%
S9	Active	2.579	0.943	100.0%
S9	Class-exclusion	3.465	1.240	100.0%

Table 3: Pairwise comparator differences in mean log-ROR.

Scenario	Difference in mean log-ROR: Active−full	Class exclusion−full	Active−class-exclusion
S1	0.018	−0.003	0.021
S2	0.019	−0.003	0.022
S3	−0.113	0.042	−0.155
S4	−0.112	0.042	−0.154
S5	−0.670	0.266	−0.935
S6	−0.099	0.027	−0.126
S7	−0.094	0.026	−0.119
S8	−0.696	0.412	−1.107
S9	−0.213	0.084	−0.297

Contrasts are differences between mean log-ROR values, not logarithms of the mean RORs.

Table 4: Signal-classification discordance across comparator strategies.

Scenario	Full vs Active	Full vs Class-exclusion	Active vs Class-exclusion
S1	2.56%	0.78%	3.02%
S2	0.08%	0.00%	0.08%
S3	22.22%	14.62%	36.24%
S4	0.00%	0.00%	0.00%
S5	98.14%	1.86%	100.00%
S6	0.00%	0.00%	0.00%
S7	0.00%	0.00%	0.00%
S8	100.00%	0.00%	100.00%
S9	0.00%	0.00%	0.00%

Table 5: Comparator-similarity sensitivity analysis.

Scenario	Comparator similarity (βB / βA)	ROR full	ROR active	Δ active−full	Signal full	Signal active
S3	0.70	1.137	1.044	−0.088	29.38%	4.88%
S3	0.90	1.122	1.004	−0.114	23.92%	2.20%
S3	0.95	1.118	0.994	−0.120	22.78%	1.78%
S4	0.70	2.259	2.077	−0.087	100%	100%
S4	0.90	2.229	1.996	−0.113	100%	100%
S4	0.95	2.221	1.976	−0.119	100%	100%

Similarity denotes the ratio of the indication coefficient for active comparator B to that for study drug A (βB / βA). Thus, 0.95, 0.90, and 0.70 represent comparator indication coefficients equal to 95%, 90%, and 70% of the study-drug indication coefficient, respectively. Higher values therefore represent greater similarity in the indication-related treatment-assignment structure.

DISCUSSION

Robustness of the comparator effect

The sensitivity analyses supported the main finding across masking strengths, and the post-freeze exploratory analyses using PRR and BCPNN. Comparator choice affected the estimate differently according to the mechanism producing the distortion. These findings are consistent with previous empirical work showing that comparator choice can change disproportionality estimates.[6,7] The simulation adds a mechanistic explanation for this heterogeneity. Under confounding, the active comparator produced a comparator-dependent change in log-ROR toward the prespecified event-generation odds ratio in both null and positive-effect scenarios. This effect persisted across the prespecified levels of comparator similarity.[8] Here, OR_{true} denotes the prespecified odds ratio governing the simulated event-generation process and is distinct from the observed ROR calculated from the simulated spontaneous reports.

The masking analysis addresses a different problem. Previous studies established masking as a source of distortion.[9,10] while the present simulation examined its effect on active-comparator designs. The resulting suppression of disproportionality was consistent with recent FAERS evidence.[11] S8 illustrates the interaction between confounding and masking. The active comparator produced changes in log-ROR toward the prespecified event-generation odds ratio in S3 and S4 but produced the lowest ROR when masking was added in S8. Thus, a comparator that performs well under one mechanism may perform poorly when another mechanism is present.[9-11]

The differential-reporting scenarios changed the continuous ROR without changing binary signal classification. This indicates that signal/no-signal status alone may not capture comparator-dependent changes in effect magnitude.

The FAERS analysis by Bai, Douros and Gravel showed that the apparent effect of removing a masking drug was greater under an active-comparator design than under a full-data comparator.[11] This is consistent with the direction of the comparator effect observed in S5 and S8, although the FAERS analysis was not a formal validation of the simulation.

The prespecified OR_{true} parameter governed the event-generation model, whereas ROR was the observed reporting disproportionality measure; these quantities were not assumed to be numerically equivalent. Scosyrev and colleagues showed that a disproportionality measure can approximate a causal rate ratio only under restrictive assumptions concerning confounding and reporting processes.[15] In our model, some of these assumptions were deliberately violated. The resulting divergence therefore reflects the reporting structure imposed in the simulation rather than a failure of the estimator.

When masking or differential reporting is plausible, the same restriction may alter the reporting background in an unfavourable direction. Accordingly, multiple defensible comparator strategies may be informative, particularly when the relevant causal and reporting mechanisms cannot be established a priori.[6,7,9-14] In practice, this supports interpreting comparator-dependent changes as part of signal triage rather than treating one reference-set definition as inherently preferable. The simulation does not establish that any comparator strategy is universally superior, nor does it estimate the magnitude of bias expected for a specific drug–event pair in a real spontaneous reporting database.

Strengths

Strengths include explicit separation of the event-generation and reporting processes, consistent comparator definitions and estimands across scenarios, inclusion of combined mechanisms, prespecified comparator-similarity sensitivity analysis, and preregistration of the protocol and code.

Limitations

The data-generating process is intentionally simplified and does not capture the full complexity of spontaneous reporting databases. The simulated class-exclusion comparator was represented by a residual background reporting state after removal of the active comparator and should therefore be interpreted as a reference-set abstraction rather than as a direct implementation of a specific pharmacological class-exclusion algorithm. The findings for this comparator should not be generalized to all empirical class-exclusion strategies. The masking parameter was intentionally strong enough to make comparator dependence observable and should not be interpreted as a typical empirical masking magnitude. Only one principal indication variable and three comparator-similarity levels were used in the confounding model.

The simulation did not incorporate all potential sources of reporting bias, including reporter-specific effects, missingness, duplicate reporting, polypharmacy, changing prescribing patterns, and correlated reporting across related products. No independent, protocol-prespecified FAERS validation case is included. The Bai et al. (2025) analysis was examined post-simulation solely as an illustrative consistency check and therefore cannot be regarded as formal external validation.

CONCLUSION

Comparator selection in pharmacovigilance signal detection should be evaluated against the mechanisms most likely to influence the reporting data. In this simulation, active comparators produced changes in log-ROR toward the prespecified event-generation odds ratio under confounding by indication but produced stronger suppression of disproportionality when masking was present. The framework may be applicable to methodological evaluations in which the effects of reference-set construction need to be separated from other sources of variation in event-generation and reporting distortion. Further empirical evaluation is required before generalizing the simulated effect magnitudes to specific spontaneous reporting databases.

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