# *Design criteria for reference sets in pharmacovigilance*

## *The case of drug-drug interactions*

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### AIM

**To explore the relative impact of various choices that can be applied to generate reference sets on the performance evaluation of three signal detection algorithms for drug-drug interaction (DDI) postmarketing surveillance.**

### INTRO

- Evaluation of signal detection algorithms (SDAs) in pharmacovigilance usually involves the use of custom-made reference sets, which are often limited in size and consider various exclusion and/or inclusion criteria.
- Each SDA, depending on the applied modelling, might be impacted to a different extent by a confounder. Hence, the performance evaluation might be biased based on the selected benchmarks, "favouring" some algorithms and penalising others.
- Detection of DDI-related signals might suffer from multiple confounders. Only limited efforts exist in the literature to generate reference sets related to two-way DDIs.

### METHODS

**Signal detection algorithms for DDI surveillance**

- *Omega*
- *delta_add*
- *Interaction Signal Score (IntSS)*

**Reference set**

- 4,455 positive controls
- 4,544 negative controls

454 drugs (RxNorm)
179 adverse events (MedDRA)

**Test data**

FAERS database (AEOLUS)

**Target metric**

Difference of Area Under the Curve (AUC) scores between restricted and unrestricted reference sets when applying each one of the design criteria.

| Design Criteria | |
|---|---|
| **A. Evidence level** (only applied to positive controls) | 1. *BNF – Study* |
| | 2. *BNF – Theoretical* |
| | 3. *BNF – Anecdotal* |
| | 4. *Micromedex – Established* |
| | 5. *Micromedex – Theoretical* |
| | 6. *Micromedex – Probable* |
| **B. Event seriousness** | 1. *EMA Important Medical Event (IME) Terms* |
| | 2. *EMA Designated Medical Event (DME) Terms* |
| **C. Event frequency** | 1. *Common AEs* |
| | 2. *Rare AEs* |
| **D. Potential confounding by indication** | |
| **E. Potential confounding by concomitant medication** | 1. *Shared indications – False* |
| | 2. *Shared indications – True* |

**Reference sets** in pharmacovigilance should be designed carefully, as restrictive **control choices** might cause **discrepant effects** between methodologies in terms of both direction and order of magnitude, hindering **fair comparative evaluation**. There is a need for **establishment of open and sizable benchmarks** that include diverse controls to ensure transparency and limit the amount of bias added to the performance evaluation.

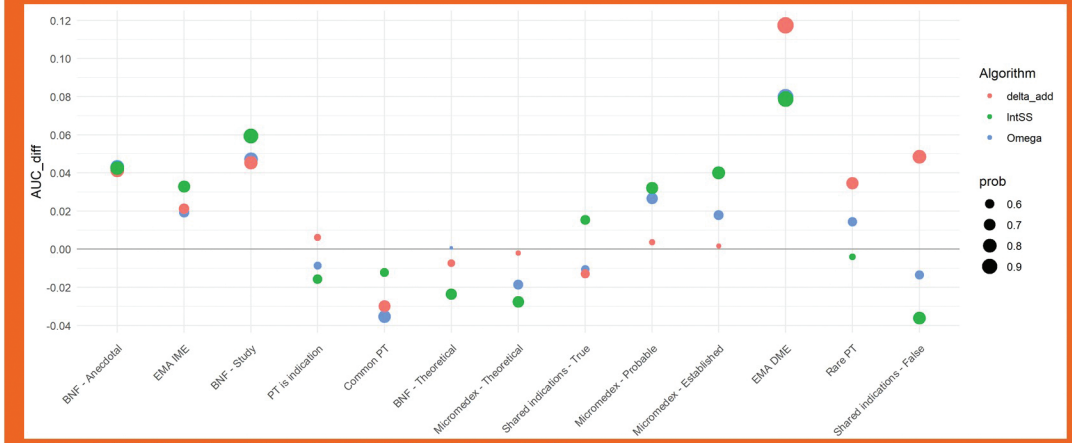


**Figure 3.** Ordered design criteria by increasing range of $AUC_{diff}$ values among SDAs.

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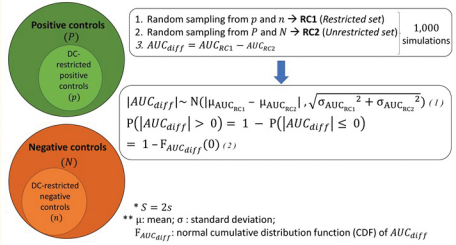


**Figure 1.** Testing framework for measuring differences in AUC scores for each design criterion.

### RESULTS

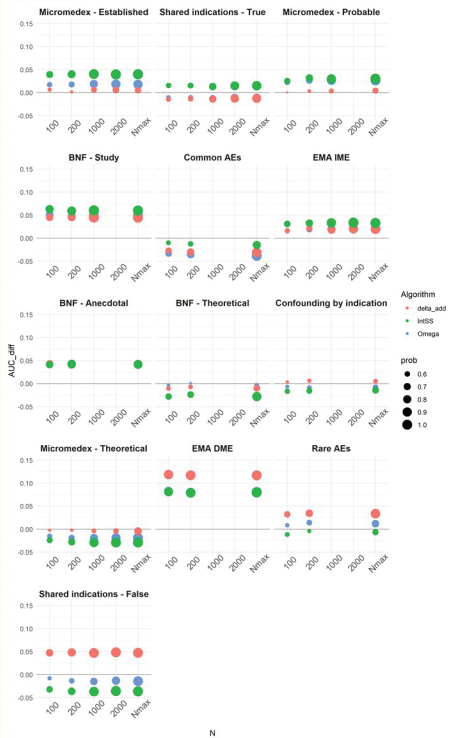


**Figure 2.** $AUC_{diff}$ values for the different design criteria, SDAs, and reference set sizes under consideration.

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