Systematic inclusion of clinical trial information as informative priors for quantitative safety signal detection in spontaneous reporting systems

Integrating clinical trial information marginally but consistently improved performance, which can reduce review burden. Further gains may be possible by refining the methodology, especially the mapping of unstructured product information between the two data sources

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Background

- Quantitative signal detection in post-marketing spontaneous reporting systems (SRSs) is crucial for drug safety surveillance. However, traditional disproportionality analyses do not include safety insights from clinical trials (CTs).[1]
- While ClinicalTrials.gov is the largest public registry of CTs, its safety data consists of non-standardized, investigator-reported text that complicates systematic analysis. The recent ClinicalTrials.gov Transformation Database pipeline[2] transforms this raw data by aligning adverse events (AEs) to the standard MedDRA terminology. This crucial step allows CT safety insights to be systematically integrated into post-marketing surveillance.
- This study proposes a Bayesian dynamic borrowing approach that integrates CT data using a robustified meta-analytic predictive (MAP) prior within a Bayesian hierarchical model, aiming to enhance AE signal detection in SRSs.

Aim

To evaluate the impact of integrating summary CT data on disproportionality analysis performance.

Conclusions

Despite generally limited impact, the CTIC approach consistently showed slightly better performance, specifically improving specificity and precision, thereby reducing review burden. A strength of this study is the use of a large reference set.

Challenging, noisy mapping between FAERS and ClinicalTrials.gov likely attenuated observable benefits. Future work will focus on improving this data mapping to better realize the method's potential. Additionally, alternative approaches for combining the data could be explored, such as varying the weight given to the clinical trial data within the Bayesian model.

Methods

ClinicalTrials.gov

Product-event pair (PE):[3] Information Component (IC) estimates from summary counts of AEs per arm within CTs

CTIC

- For each specific PE, IC estimates from CTs are used to create a MAP prior.
- This prior is then combined with FAERS data (2015–2019) for the same pair within a Bayesian model to generate statistical alerts.

product name
reported name
active moiety in group title or description

Mapping between ClinicalTrials.gov and FAERS

- CTs exclusion:
  - CT arms mapped to several products
  - arms mapped to both "placebo" and a product
  - CTs lacking at least one exposed arm and one placebo arm

48 products included in the evaluation

Performance evaluation

Traditional IC[4] vs CTIC

Published reference set[3]
- 88 products approved between 2014 and 2017

Results

96293 PE reported in FAERS – 88 products

5697 (5.9%) FAERS PE with available data in ClinicalTrials.gov – 48 products

4898 (5.1%) Reference PE with available data in ClinicalTrials.gov and FAERS

Traditional IC vs CTIC

	Traditional IC	CTIC
Precision	217/962 = 0.23	222/911 = 0.24
Sensitivity	217/973 = 0.22	222/973 = 0.23
Specificity	3180/3925 = 0.81	3236/3925 = 0.82

F1-score: Traditional IC 22.4% vs CTIC 23.6%

ROC AUC: Traditional IC 51.7% vs CTIC 52.6%

- One selected product demonstrated a 19% difference in F1-score favoring CTIC, with true positives detected 2.7 years sooner on average.
- 4767 out of 4898 (97.3%) PE showed consistent results between traditional IC and CTIC.

Abbreviations

CTIC, clinical trial information component; **FAERS**, US Food and Drug Administration Adverse Event Reporting System; **MedDRA**, Medical Dictionary for Regulatory Activities; **ROC AUC**, receiver operating characteristics area under curve.

References

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Data Sharing Statement

The data that support the findings of this study are available from the corresponding author (FH), upon reasonable request.

Authors' contributions

Study concept and design: FH, JP, GP, and AB. Data acquisition: FH and JP. Data analysis: FH and JP. Data interpretation: FH, JP, GP, and AB.

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