Abstract number 1762550

An Application of Bayesian Modelling for Information Sharing in Safety Signal Detection

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Disclosures: All authors are employed by GSK and hold financial equities in GSK. All authors declare no other financial or non-financial interests, relationships and activities.

Conclusions

- In our experiment, the Bayesian borrowing allows for better and faster detection of some labelled events.
- The borrowing methodology and MedDRA levels chosen have a major impact on the results and demonstrate the importance of using a sensible ontology with respect to the analysis.
- Further work is required to finetune the HMMs and employ a suitable ontology.

Background

- The multi-item gamma Poisson shrinker (MGPS) is a quantitative approach used routinely for safety signal detection in spontaneous reporting systems. It highlights statistical alerts for clinical review as potential signals based on Bayesian shrinkage of an observed-to-expected (O/E) ratio, H0 being independence between drug and AEs.
- MGPS treats AE MedDRA PT as independent, not allowing for clinical similarity of AEs, leading to potential false negative alerts (dilution) and false positive spurious findings. Berry and Berry[1] addressed this challenge in clinical trial data with a three-level hierarchical mixture model (HMM), borrowing strength of association across MedDRA SOC.

Aims

Bayesian HMM vs MGPS

FAERS data

Methods

FAERS data: Test case: Zolpidem | Time period*: 2004Q1 → 2009Q4 (Bayesian HMM analysis / MGPS analysis) → Detection of AEs (at PT level)

Methods used:

Bayesian HMM analysis (new approach, performed using JAGS[2])

Borrowing at the MedDRA high level group term
- Logarithm of odds ratio (OR)
- Alert = P5 >1 of OR posterior distribution

MGPS[3] (traditional approach)
- Bayesian shrinkage of an O/E ratio distribution
- Alert = EB05 >1 (lower limit of credibility interval)

*Due to computational complexity, the data was restricted to this period which still provides a representative, historical lookback of data.

Evaluation of performance using both methods: Bayesian HMM vs MGPS

Time to detection of true positives (TP)
- Quarterly analysis: 2005Q1 – 2009Q4
- TP: labelled AEs from the latest published version of SIDER (2015)[4]

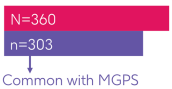
Results

All data in 2009Q4:

886 PTs tested

Bayesian HMM vs MGPS

Alerts generated



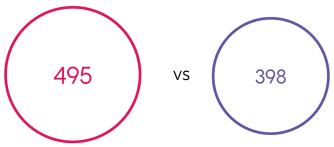
Common with MGPS

Common with Bayesian HMM

PPV

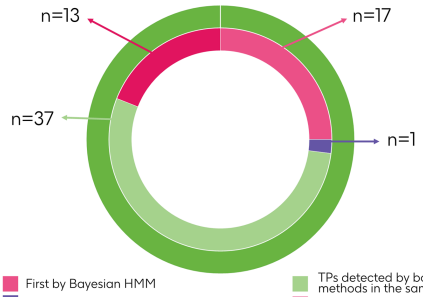
In quarterly analysis:

Alerts generated (some appearing and disappearing)

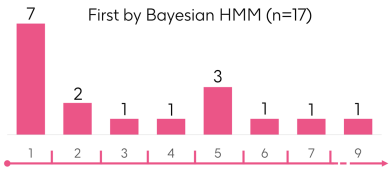


Time to detection of TPs (quarterly analysis)

Total detected TPs (N=68)



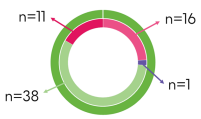
First by Bayesian HMM (n=17)



Bayesian HMM with borrowing at MedDRA SOC level and HLT (sensitivity analysis)

SOC level: detected TPs (N=65)

HLT: detected TPs (N=66)



Abbreviations

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SOC: system organ class; FAERS: FDA (US Food and Drug Administration) AE reporting system; PPV: positive predictive value; HLT: high-level term.

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Acknowledgements

Medical writing (Maria C. Maior) and coordination support were provided by Akkodis Belgium c/o GSK.

Funding

GSK

Digital poster

ISPE | 24–28 August 2024 | Berlin, Germany

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