Leveraging the natural structure of adverse events for signal detection in randomised controlled trials: a review of statistical methods

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BACKGROUND

- **Signal detection:** in randomised controlled trials with efficacy-related primary outcomes, we analyse safety data with the aim to detect signals indicating that an adverse event could potentially be an adverse reaction (i.e. reasonable causal link with intervention).
- **Challenges**: achieving a delicate balance between inflated false positive rates, due to multiple testing, and high false negative rates, due to overly conservative adjustments on outcomes that trials were never powered on.
- **Aims of this work**: identify all existing statistical methods leveraging the natural structures within the coding of adverse events (e.g. through the MedDRA hierarchy), an innovative strategy to increase power while managing multiplicities.

METHODS

- **Scoping review of the methodological literature,** with a **systematic search** of the Embase, MEDLINE, Scopus and Web of Science databases conducted in February 2023
- **Extraction** of methodological characteristics, **review** of analyses approaches, **categorisation** of the methods and **narrative summary** of the findings

RESULTS

18 STATISTICAL METHODS USING GROUPINGS OF ADVERSE EVENTS FOR SIGNAL DETECTION

7 ERROR CONTROLLING PROCEDURES *or methods conducting significance tests only*

11 BAYESIAN MODELING APPROACHES *or methods producing treatment effect estimates*

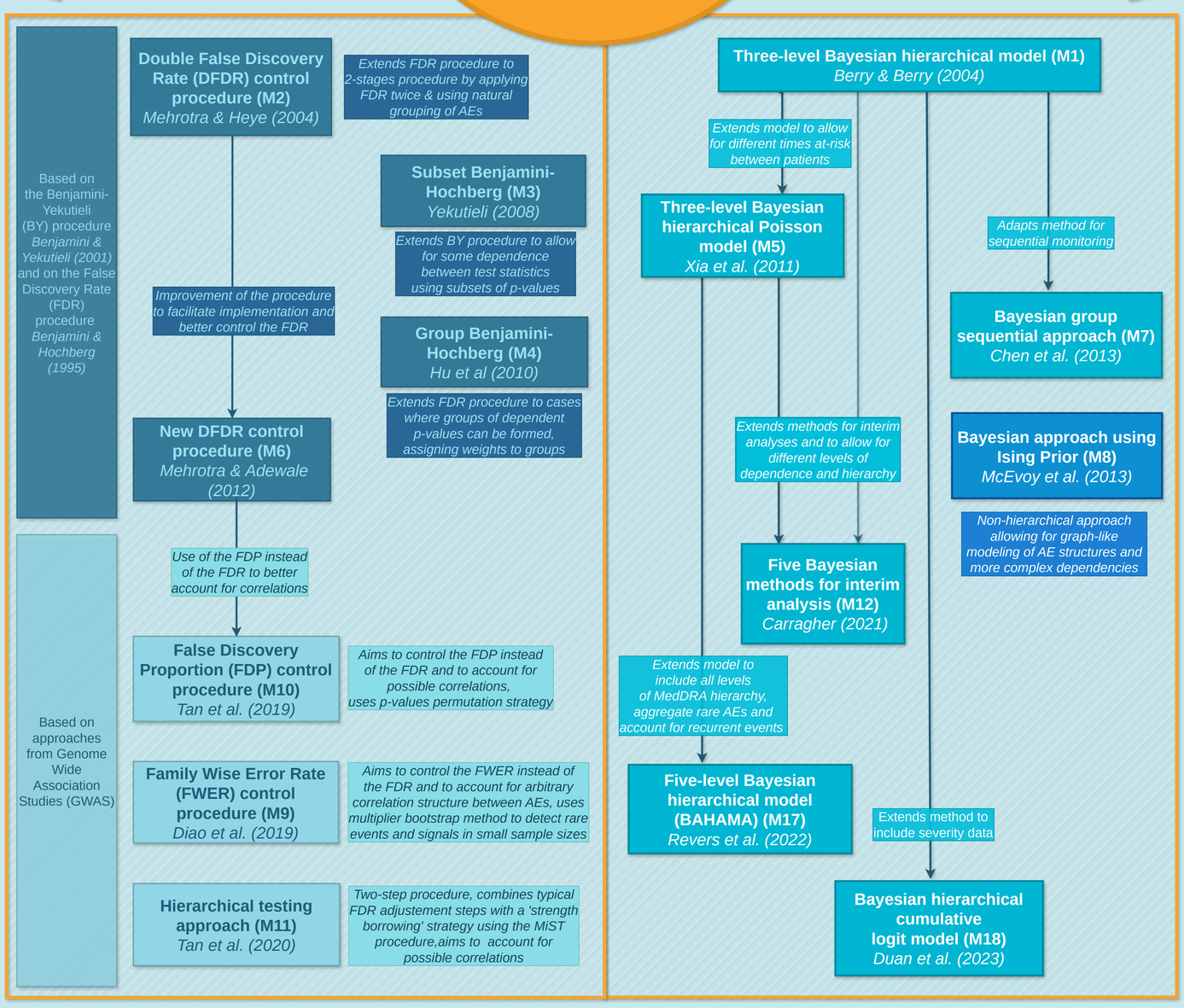


Fig. 1: Diagram representing families of methods and detailing how they relate to each other

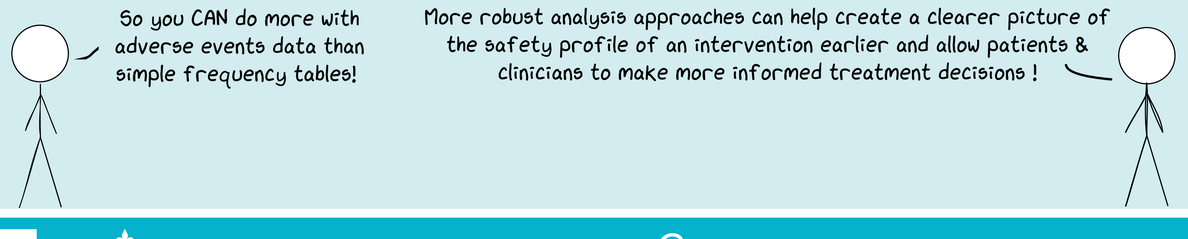
Key methodological characteristics	Classification		Number of methods
Type of outcomes	Binary		10 (M1, M2, M3, M4, M6, M7, M8, M9, M10, M11)
	Binary, adjusted for time-at-risk		6 (M5, M12-M16)
	Binary and ordinal		1 (M18)
	Counts		1 (M17)
Nature of the data	Patient-level data		3 (M9, M10, M11)
	Summary data		15 (M1, M2, M3, M4, M5, M6, M7, M8, M12-M16, M17, M18)
Type of analysis	Interim analyses		6 (M7, M12-M16)
	Final analysis		12 (M1, M2, M3, M4, M5, M6, M8, M9, M10, M11, M17, M18)
Restrictions on the events considered	Common AEs only		3 (M1, M2, M6)
	None specified, all AEs		15 (M3, M4, M5, M7, M8, M9, M10, M11, M12-M16, M17, M18)
Structure of the Bayesian modeling approaches	Fixed hierarchical structure	2 levels	10 (M1, M2, M3, M4, M6, M7,M8, M9, M10, M11)
		3 levels	6 (M5, M12-M16)
		5 levels	1 (M17)
	Complex graph-like structure		1 (M8)

Table 1: Summary of methodological characteristics by methods

55% of the 18 methods identified were published since 2019

OTHER RESULTS

- **A majority of the methods (n=16) only used binary outcomes:** it is common in adverse events analysis for the full extent of information collected not to be used
- Most methods were developed by **authors with affiliations to universities** only (n=11) or partly (n=7).
- **Little comparability** possible between simulations run across different sources to appraise methods



CONCLUSIONS

- A **large number of existing methods** making use of the natural structures within adverse events data were identified, with a **diversity of methodological characteristics.**
- Applied statisticians are faced with a large choice of different methods, but **lack of evidence and guidance** regarding their suitability for different scenarios.
- The rapid increase in methods development highlights a growing awareness that methodological improvements in this area are needed - but **whether these advancements are adopted into practice** has not yet been established.
- **Further objective appraisals** of these methods and development of guidance on optimal analysis approaches are **needed to create effective change in practice.**

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Illustration source: pixabay.com

[1] European Medicines Agency.: Adverse event. Accessed 21st March 2024.Available from: https://www.ema.europa.eu/en/glossary/adverse-event.