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Methods in Reducing Drug–Drug Interactions in Inappropriate Prescribing: A Systematic Review Protocol

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202630031

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 9 March 2026 and was last updated on 9 March 2026.

INTRODUCTION

Review question / Objective 1. What models or tools have been developed to reduce Drug-drug interactions (DDIs) in managing inappropriate prescribing? 2. How do the developed models or tools measure the reduction of DDI? 3. Do the more complex artificial intelligence (AI)-driven models have better performance versus simpler policy-driven models?

Rationale DDIs remain a major contributor to preventable patient harm, particularly within the context of polypharmacy and multimorbidity. As prescribing complexity intensifies, the resulting information burden increasingly challenges the boundaries of human-centric decision-making. Over the past two decades, interventions to mitigate inappropriate prescribing have evolved from deterministic rule-based clinical decision support systems toward stochastic and AI-driven predictive models.

While deterministic systems emphasize workflow optimization, alert management, and ontology-based rule enforcement, newer models incorporate high-dimensional datasets, probabilistic modeling, and generative architectures. However, it remains unclear whether methodological complexity yields proportional improvements in clinically reliable medication safety. This review will synthesize evidence across deterministic and stochastic domains to evaluate whether advances in computational sophistication translate into meaningful improvements in DDI mitigation.

Condition being studied 1. Any method, tools, or model used in addressing inappropriate prescribing related to DDIs.
2. Medication errors specifically attributable to DDIs within clinical prescribing contexts.

METHODS

Search strategy A structured search strategy will be developed using predefined keywords and

Boolean operators across four conceptual domains:
("Inappropriate prescri*" OR "Medication error" OR "prescri* error reduction" OR "Prescribing error")
AND
("Drug-Drug Interaction" OR Polypharmacy OR "Drug Interaction")
AND
(Optimization OR Optimi* OR Improve* OR Reduc*)
AND
("Clinical decision support" OR CDSS OR "Electronic prescri*" OR e-prescri* OR "Decision support system" OR "Predictive model" OR "Rule based" OR "Guideline based" OR Algorithm OR "Artificial intelligence" OR AI OR "Machine learning" OR "Deep learning" OR "Data-driven model" OR "Automated system" OR "Hybrid model" OR "Medica* Pathway")
Search syntax will be adapted for each database.

Participant or population Inclusion: 1. Studies conducted in real-world clinical settings, not restricted to any settings, including hospitals, outpatient care, geriatric wards, home care environments, and intensive care units. 2. Simulated clinical environments or pilot implementations of prescribing systems. 3. Computational datasets derived from electronic health records, structured medication databases, or large-scale biomedical repositories. 4. Synthetic datasets used for model development and validation. 5. No demographic restrictions will be imposed.
Exclusion: 1. Studies focusing exclusively on dispensing, medication administration, or diagnostic populations without prescribing decision context.

Intervention Inclusion: 1. Interventions targeting inappropriate prescribing related to DDIs. 2. Computational or clinical systems designed to detect, predict, prevent, or optimize mitigation of DDIs. 3. Interventions addressing DDI-related prescribing errors, polypharmacy risk, or medication safety within prescribing workflows.
Exclusion: 1. Studies addressing non-DDI medication errors (e.g., dispensing errors, administration errors). 2. Studies exclusively focus on disease diagnosis or non-prescribing clinical decision support.

Comparator Not applicable.

Study designs to be included Inclusion: 1. Development, validation, or implementation of computational, statistical, or algorithmic models for safe prescribing. 2. Deterministic rule-based systems. 3. Ontology-based or guideline-based frameworks. 3. Artificial intelligence-driven predictive models, including machine learning, deep learning, graph-based models, and generative large language models. 4. Hybrid or ensemble model integrating any previous design.Exclusion: 1. Studies using computational tools solely for diagnostic classification without prescribing optimization. 2. Purely theoretical models without application.

Eligibility criteria Inclusion: 1. Model development and evaluation studies. 2. Literature reporting validated computational models.

Information sources Electronic databases: PubMed, Scopus, ScienceDirect, IEEE Xplore. All reference lists of eligible studies will be screened manually.

Main outcome(s) 1. Reduction in drug-drug interactions or inappropriate prescribing events. 2. Improvements in prescribing process measures (e.g., alert optimization, workflow improvements). 3. Performance metrics of the models (e.g., AUC, RMSE, Jaccard similarity, accuracy, f-1-score, hit rate, or any other reported).

Additional outcome(s) 1. Model validation procedures (internal, cross-validation, external validation). 2. Reporting of calibration and overfitting handling. 3. Applicability to real-world clinical contexts.

Data management Data will be extracted independently using a standardized extraction form.

The following variables will be collected:

1) Study characteristics: author, year, country, study design.
2) Population characteristics: settings, specialty, specifications, size.
3) Model: name, classification, aim.
4) Performance Metric: measures, performance values, scores, descriptive outcomes.
5) Comparator: metrics for comparator, validation criteria.
6) Data: data source, type of data.

Quality assessment / Risk of bias analysis Risk of bias will be assessed using the Prediction Model Risk of Bias Assessment Tool-AI (PROBAST+AI), a version of PROBAST extended with artificial intelligence-specific considerations. Key domains will be evaluated accordingly. If the majority (more than 50%) of the sub-domain reported as 'low', the key domain will be judged as low risk of bias; if the

majority (more than 50%) of the subdomain is marked 'high', the key domain will be judged as high risk of bias. A key domain will be judged as 'unclear' if mixed finding is reported. For the planned review, the following core key domains will be used to determine the overall risk of bias for the included study: [1] Participants and Data Source. [2] Predictors. [3] Outcomes. [4] Analysis.

Strategy of data synthesis Findings will be synthesized narratively due to anticipated heterogeneity in outcome measures and study designs. Studies will be grouped according to intervention types, namely:
Clinical-policy vs Ontology vs AI-driven. Rule based vs CDSS. Broad policy level vs Patient specific measures.
Meta-analysis will only be conducted if suitable data are available and sufficient homogeneity in outcome measures is observed.

Subgroup analysis Where applicable, subgroup analysis may be conducted based on:

1. Intervention type
2. Dataset type (clinical vs synthetic)
3. Model architecture
4. Evaluation of metric category
5. Clinical setting.

Sensitivity analysis Wherever applicable, sensitivity analyses will be performed by excluding studies at high risk of bias or those lacking external validation.

Language restriction Only studies published in English will be considered due to restricted resources.

Country(ies) involved Malaysia - National Defence University of Malaysia.

Keywords inappropriate prescribing; drug-drug interaction; clinical decision support; artificial intelligence; policy-driven; systematic review protocol.

Contributions of each author
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