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Leveraging Real-World Evidence to Extend Drug-Drug Interaction Assessment from Drug Development to Clinical Care: A Targeted Review of the Literature

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Background & Objective

- Drug-drug interactions (DDIs) can impact the effectiveness, safety, and value of drugs.
- DDI patterns can vary across different healthcare systems and patient populations.
- Evaluating DDIs in a real-world setting is key to accurately assess the clinical and economic outcomes of drugs.
- Real-World Data (RWD) can help in:
  - ✓ Identifying potential DDIs
  - ✓ Assessing their clinical significance
  - ✓ Guiding dose adjustments to manage potential DDIs
  - ✓ Supporting overall benefit-risk assessment of drugs or drug combinations
- This literature review aimed to characterize current applications of RWD in evaluating and mitigating DDI risks, while identifying gaps to be addressed.

Methods

- A targeted literature search was performed in PubMed using a combination of key words including "drug interactions" and "real-world". The search was supplemented with gray literature and manual searches.
- Identified publications were reviewed and key findings related to the use of real-world evidence (RWE) to inform DDI assessment were summarized.

Results

- A total of 132 studies were included in the review (**Figure 1**).

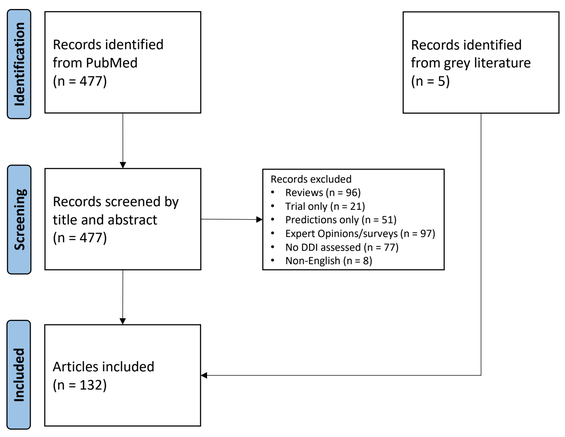

Figure 1. *PRISMA Flowchart*

Study design

- Real-world data were predominantly from electronic health records; half of the studies were cohort studies (**Figure 2**).

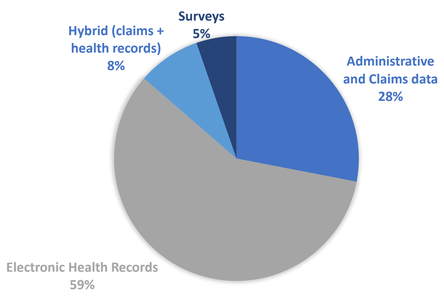

Figure 2. *Data source*

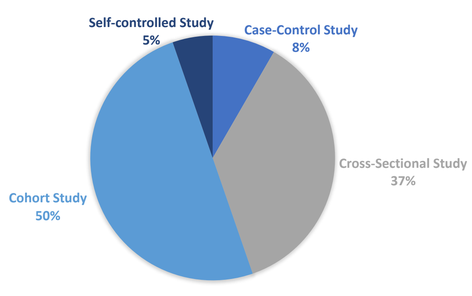

Figure 3. *Study design*

DDI assessment

- Of the 132 studies included, 44% focused on identifying comedications that are potentially subject to DDIs. The remaining studies aimed to assess the clinical impact of concomitant drugs; in some cases (17%), this was the primary objective of the research, while in others (39%), the assessment of clinical impact was conducted alongside an analysis of the prevalence of comedication use.
- Among studies evaluating the clinical impact of DDIs, the primary outcome considered was mostly a safety outcome (**Figure 4**).
- The DDI involved included a pharmacokinetic component for 67% of the studies (**Figure 5**).

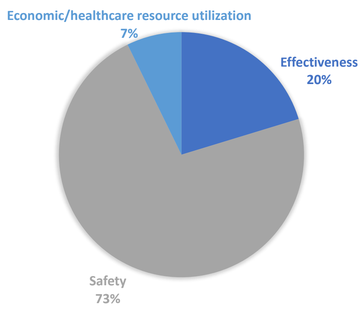

Figure 4. *Primary outcome assessed*

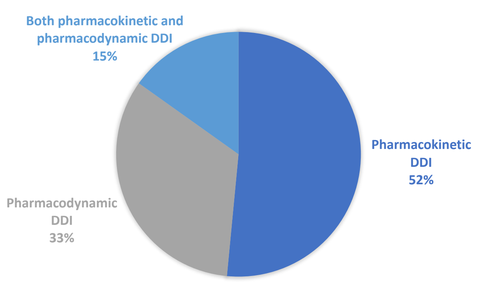

Figure 5. *Type of DDI involved*

Results (ctd)

- The studies reviewed encompassed several key areas beyond the identification of potential DDIs and their clinical impact. A notable proportion of studies described applications of the generated RWE for regulatory purposes, as well as strategic and modelling frameworks based on RWD to predict DDI risks and support decision making. **Table 1** summarizes the use cases of RWE in the DDI landscape.

Table 1. *Overview of RWE use cases in the DDI landscape*

Overall objective	Objective	Insight/evidence generated	Impact
Guide DDI Assessment	Determine the frequency and treatment duration of concomitant medication use in the target patient population	Informed realistic DDI evaluations based on the target patient population in the real-world setting and informed inclusion/exclusion criteria of concomitant medications use for patient studies	Design of clinical trials
	Identify and evaluate novel DDIs with RWD analysis	Identification of new drug–drug pairs with increased risk of safety event, thus indicating clinically relevant DDIs	Design of clinical trials
	Identify transporter-mediated DDIs real-world data	Risk mitigation measures put in place for specific subpopulations	Inform risk management materials
Complement/validate model-based predictions regarding clinical impact of DDIs	Demonstrate the potential utility of RWD to assess model-based predictions as part of a drugs life cycle management	Exposure-risk relationship observed with RWE substantiate claims made from PBPK models	Reinforce evidence from modelling
Contextualize findings	Study similarities/differences in treatment patterns according to healthcare systems	Knowledge on how DDI patterns and prevalence vary across different healthcare systems and patient populations allows to account for these differences to provide accurate, context-specific insights on the clinical and economic impact of DDIs	Inform HEOR research

- The supplementation of DDI research with RWE is depicted in **Figure 6**.

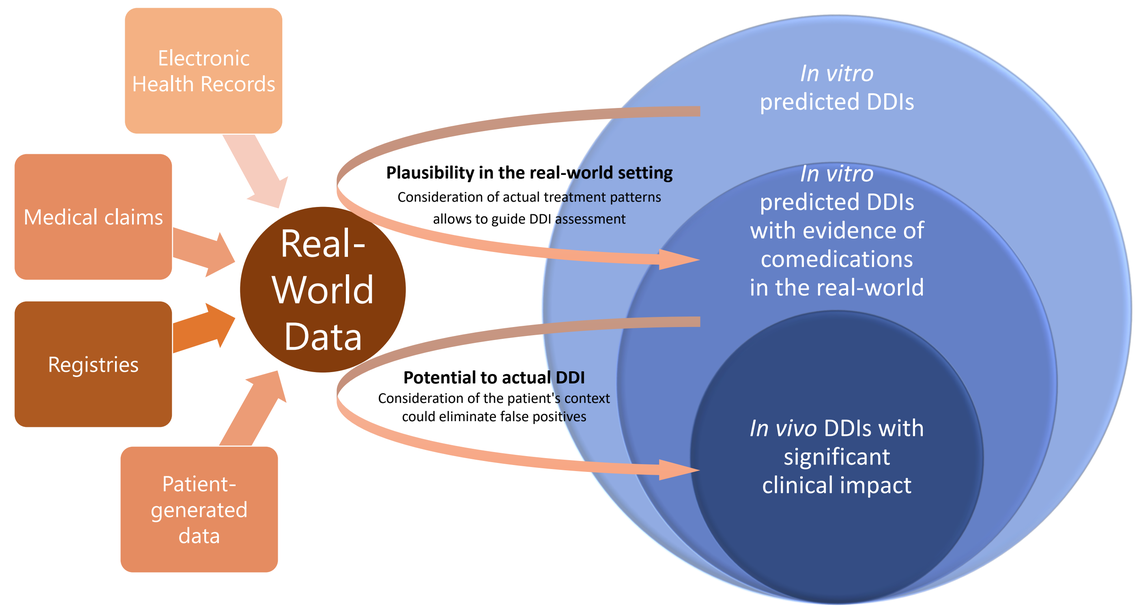

Figure 6. *Strengthening DDI research with RWE*

- A general framework for the use of RWE in DDI evaluations during the drug development process is proposed in **Figure 7**.

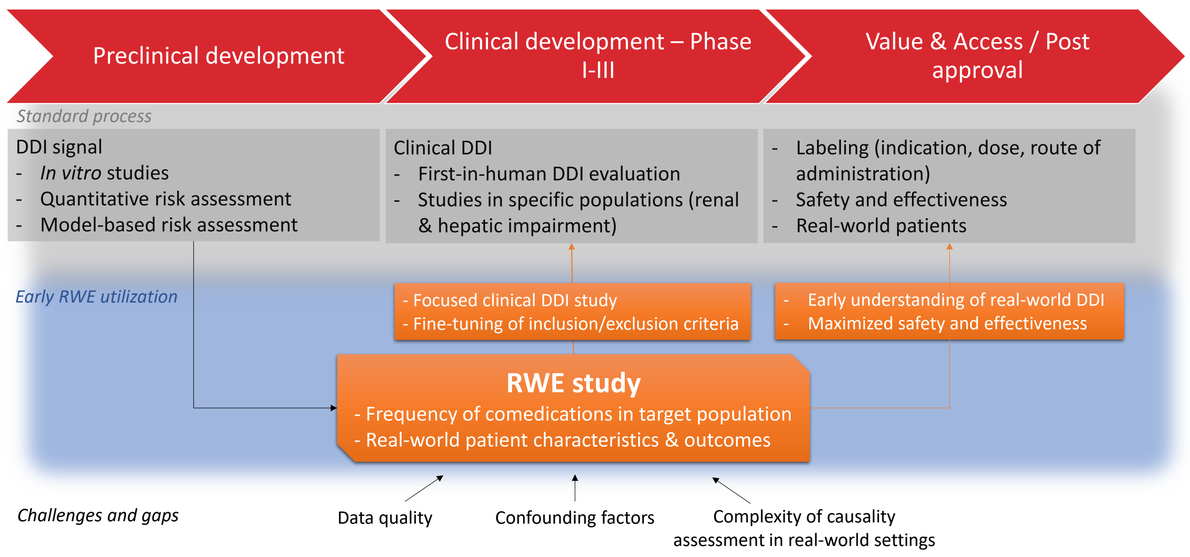

Figure 7. *Proposed framework for the use of RWE in DDI evaluations*

Conclusions

- This review highlights how RWE has been used to complement and support DDI research and surveillance.
- In addition to the significant use of RWD to identify potential DDIs and understand the clinical impact of DDIs in a real-world setting, this study also underlines the increasing interest of regulatory agencies in RWD to support decision making, hence warranting "regulatory grade" RWE on DDIs.
- Developing robust methodological frameworks is key to ensure the quality, relevance, and appropriate use of RWD for DDI assessments to support drug development, market access, and clinical decision-making.

References

1. FDA, Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products (Aug. 2023), https://www.fda.gov/media/171667/download.
2. Zhao X, Iqbal S, Valdes IL, Dresser M, Girish S. Integrating real-world data to accelerate and guide drug development: A clinical pharmacology perspective. Clin Transl Sci. 2022 Oct;15(10):2293-2302. doi: 10.1111/cts.13379.
3. Zhu R, Vora B, Menon S, et al. Clinical pharmacology applications of real-world data and real-world evidence in drug development and approval-an industry perspective. Clin Pharmacol Ther. 2023; 114: 751-767. doi:10.1002/cpt.2988