Addressing Information Bias in EHRs and Claims Data: What Can the Literature Tell Us and How Should We Respond?

ISPOR 2025 | Montréal, QC, Canada | Friday, May 16, 8:00 - 9:00 AM

Patrick Arena, PhD | Aetion, Inc.

Disclosure

- Employee of and has stock options in **Aetion, Inc.**, which works in collaboration with several pharmaceutical companies, government organizations, and payers in healthcare
- Previous contractor for **Pfizer, Inc.**

RWE guidances from across the world

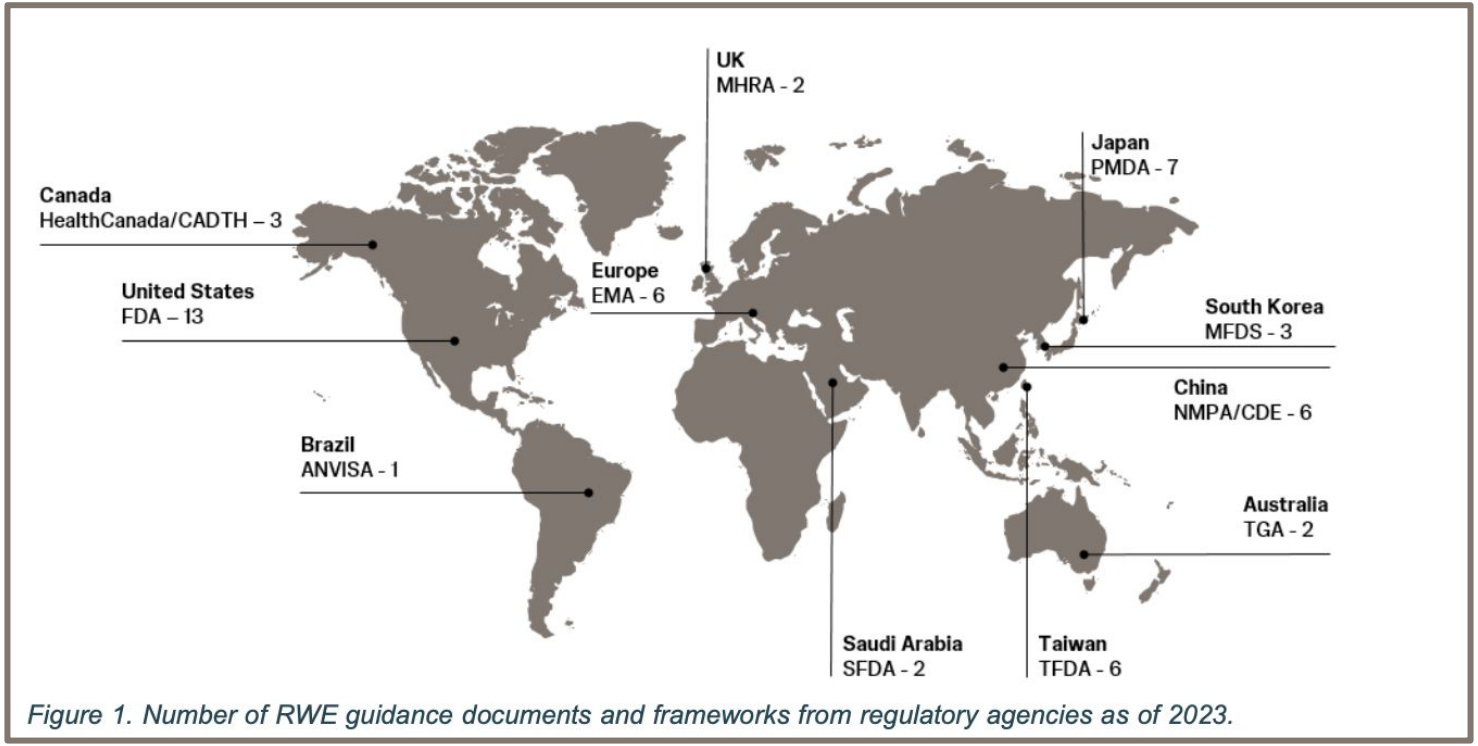

Figure 1. Number of RWE guidance documents and frameworks from regulatory agencies as of 2023.

Sources: IDERHA's D6.2 Report on Global Regulatory Best Practices Analysis: A scoping review of HTA and Regulatory RWD/RWE policy documents; Duke-Margolis Institute for Health Policy's RWE Collaborative's International Harmonization of Real World Evidence Standards Dashboard.

The rise of RWE studies to support decision-making

> Clin Pharmacol Ther. 2022 Jan;111(1):135-144.
doi: 10.1002/cpt.2474. Epub 2021 Nov 22.

The Role of Real-World Evidence in FDA-Approved New Drug and Biologics License Applications

Christina A Purpura [1], Elizabeth M Garry [1], Nicholaas Honig [1], Abigail Case [1], Jeremy A Rassen [1]

"In this study, we detailed how over the past 2.5 years, both the quantity of RWE submitted and its impact on FDA's decision making—particularly as supportive evidence—have significantly increased"

Editorial > J Comp Eff Res. 2023 Nov;12(11):e230135.
doi: 10.57264/cer-2023-0135. Epub 2023 Oct 19.

The real-world impact of National Institute for Health and Care Excellence's real-world evidence framework

Stephen Duffield [1], Páll Jónsson [1]

"While the direct analysis of real-world data for comparative effects estimation remains in its infancy for appraisals of medicines, it's playing an increasingly influential role"

Review > Clin Transl Sci. 2024 Aug;17(8):e13903.
doi: 10.1111/cts.13903.

Real-world evidence to support regulatory submissions: A landscape review and assessment of use cases

Golnoosh Alipour-Haris [1 2], Xinyue Liu [2], Virginia Acha [2], Almut G Winterstein [1], Mehmet Burcu [2]

"The findings illustrated a broad distribution of RWE application across different therapeutic areas…[and that] the use of real-world external controls in interpretation of results from single-arm trials has gained prominence"

Sources: Purpura et al. The Role of RWE in FDA-Approved New Drug and Biologics License Applications. Clin Pharmacol Ther. 2022. Duffield & Jónsson. The real-world impact of NICE's RWE framework. J Comp Eff Res. 2023. Alipour-Haris et al. RWE to support regulatory submissions: A landscape review and assessment of use cases. Clin Transl Sci. 2024.

RWE bias concerns raised by regulators/HTA bodies

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The Role of Real-World Evidence in FDA-Approved New Drug and Biologics License Applications

Christina A Purpura [1], Elizabeth M Garry [1], Nicholaas Honig [1], Abigail Case [1], Jeremy A Rassen [1]

"Across all documented studies, the issues noted in FDA's feedback were methodological issues, sample size concern, omission of patient-level data, and other limitations"

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The real-world impact of National Institute for Health and Care Excellence's real-world evidence framework

Stephen Duffield [1], Páll Jónsson [1]

"Non-systematic identification of data sources, unclear curation processes, and complex and opaque study designs lead to general concerns over data suitability for the research question of interest and risk of bias"

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Real-world evidence to support regulatory submissions: A landscape review and assessment of use cases

Golnoosh Alipour-Haris [1 2], Xinyue Liu [2], Virginia Acha [2], Almut G Winterstein [1], Mehmet Burcu [2]

"Major common themes of limitations included small sample size, selection bias, missing data, *misclassifications*, and confounding"

Sources: Purpura et al. The Role of RWE in FDA-Approved New Drug and Biologics License Applications. Clin Pharmacol Ther. 2022. Duffield & Jónsson. The real-world impact of NICE's RWE framework. J Comp Eff Res. 2023. Alipour-Haris et al. RWE to support regulatory submissions: A landscape review and assessment of use cases. Clin Transl Sci. 2024.

RWD & the potential for information bias

Real-world data sources (e.g., EHRs and administrative claims data) are **collected for purposes other than research** and represent routine clinical care

Patient has symptoms, acute illness, etc. ➡ **Encounter with healthcare professional** ➡ **Examination, history, diagnostics**

Adapted from Schneeweiss S & Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol. 2005;58(4):323-337.

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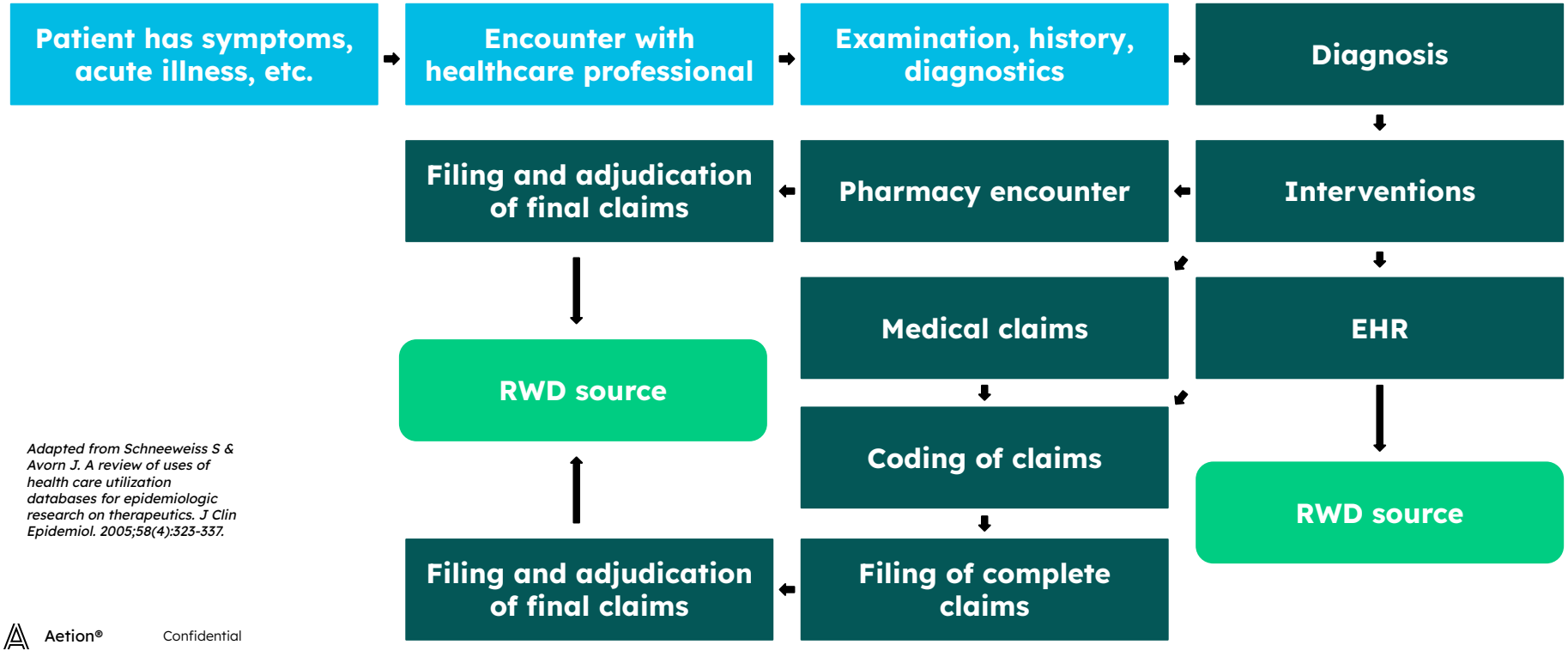

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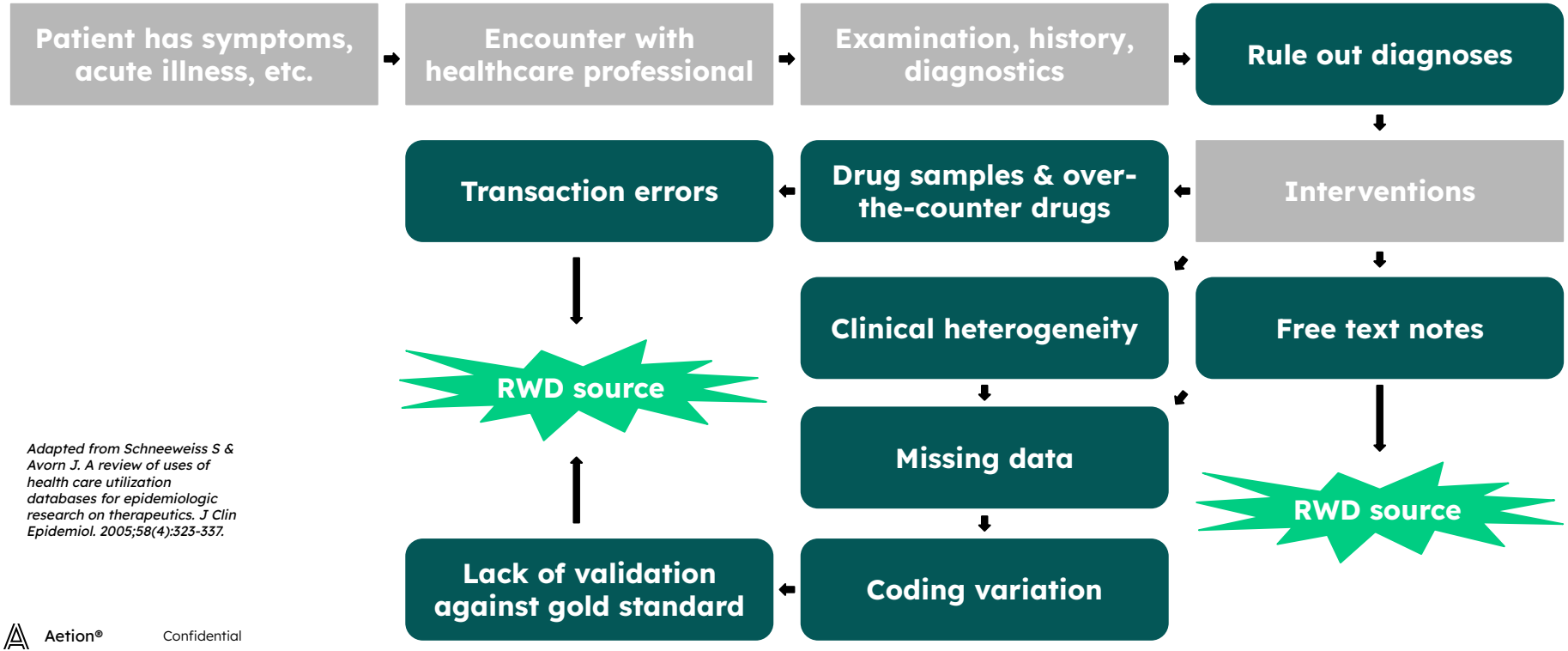

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RWE studies & the potential for information bias

Real-world evidence studies can thus be prone to **information bias**

Table 3 Methodological characteristics of the reviewed studies

Methodological characteristics	Total (*N* = 75)	Cohort studies (*N* = 65)	Case-control studies (*N* = 10)
Nonuser comparator,[a] *n* (%)	41 (55)	31 (48)	10 (100)
Prevalent-user design, *n* (%)	38 (51)	28 (43)	10 (100)
Major methodological issues			
Time-related bias (i.e., immortal person-time in cohort studies, time-window bias in case-control studies), *n* (%)	43 (57)	41 (63)	2 (20)
Adjustment for postbaseline variables without appropriate statistical models, *n* (%)	31 (41)	21 (32)	10 (100)
Depletion of outcome-susceptible individuals, *n* (%)	33 (44)	23 (35)	10 (100)
Reverse causation, *n* (%)	29 (39)	25 (38)	4 (40)
Number of major methodological issues per study, median (IQR)	2 (1–3)	2 (1–3)	2.5 (2–3)
Detection bias, *n* (%)	16 (21)	11 (17)	5 (50)
Exposure misclassification, *n* (%)	23 (31)	21 (32)	2 (20)
Outcome misclassification, *n* (%)	8 (11)	7 (11)	1 (10)
Informative censoring, *n* (%)	6 (8)	6 (9)	0 (0)

Source: Bykov K et al. Prevalence of Avoidable and Bias-Inflicting Methodological Pitfalls in Real-World Studies of Medication Safety and Effectiveness. Clin Pharmacol Ther. 2022;111(1):209-217.

Addressing information bias

Prior literature reviews have offered information bias mitigation methods recommendations

Regulatory and health technology assessment guidances also recommend “standard” practices (e.g., chart validation) to mitigate the impact of information bias

But information bias continues to remain a threat to RWE studies…

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The next three presentations will provide an overview of information bias in RWD studies so that we can learn more about current strategies for information bias mitigation and potential paths forward for best practices

- *Allan Meng - insights from a targeted review of information bias in EHRs and claims data*
- *Daina Esposito - improving studies through study design and other methods*
- *Mina Tadrous - the power of linkage and the Canadian perspective*

Thank you!

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