



International Society
for Pharmacoepidemiology

ISPE'S POSITION ON REAL-WORLD EVIDENCE (RWE)

February 12, 2020

As the international society for the study of the use and effects of medicines and other health interventions in human populations, the International Society for Pharmacoepidemiology (ISPE) has contributed to the development of methods, policy, education, and advocacy for the field of pharmacoepidemiology for over 30 years. Its members appreciate the opportunities and challenges in the use of real-world data (RWD) collected as part of routine clinical care for generating **real-world evidence (RWE)** intended for patient, clinical, payer, and regulatory decision-making. ISPE applies robust epidemiological, causal inference, and data science methods to RWD studies that may utilize sources such as electronic health records (EHRs), administrative databases, registries, or other primary and secondary data collection approaches.

Randomized controlled trials (RCTs) have served and will continue to serve as the major evidentiary standard for regulatory approvals of new molecular entities and other health technology. Nonetheless, **RWE derived from well-designed studies, with application of rigorous epidemiologic methods, combined with judicious interpretation, can offer robust evidence regarding safety and effectiveness.** Such evidence contributes to the development, approval, and post-marketing evaluation of medicines and other health technology. It enables patient, clinician, payer, and regulatory decision-making when a traditional RCT is not feasible or not appropriate. Importantly, RWD studies may address known limitations of RCTs by studying patient outcomes in routine clinical practice, often with long follow-up. Such studies may, in certain circumstances, offer a more efficient and clinically relevant alternative to traditional RCTs. Sometimes they are the only practical or ethical way to study a specific research question. While regulatory agencies have relied on RWE for post-marketing safety evaluations for many years, and health technology assessment and health insurance agencies have considered RWE in reimbursement and coverage decisions, it is encouraging to see regulatory agencies now considering RWE, including pragmatic randomized clinical trials (pRCTs), to support new indications, labeling changes, and for approval of new products in some circumstances.

Many ISPE members have contributed to public and private initiatives involving RWD and RWE, thus helping set the data and methodological standards for post-market assessment, monitoring, and reporting of medical product safety and effectiveness. Pharmacoepidemiologists as experts in RWE can identify the specific settings in which causal inference is possible in the absence of randomization and protocol-based outcomes ascertainment. Generation of RWE relies on observational research methods. ISPE members have been pioneers in developing and





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implementing study designs and methodologies for valid causal inference, as well as identifying and offering solutions regarding biased designs. Some examples include marginal structural models, methods to address time-related biases, self-controlled designs, cluster randomized trials, pRCTs, and hybrid studies with both randomized and non-randomized/observational components, or those that use both primary and secondary data. Furthermore, our members have been leaders in methods for the use of RWD as external controls for single-arm or other long-term extension trials, the use of negative controls for exposures and outcomes, validation studies of study outcomes or exposures, propensity score and other methods to control for measured and unmeasured confounding, new/prevalent user cohort and other innovative study designs. These designs can be applied to both safety and comparative effectiveness questions.

ISPE, through its members' expertise in epidemiologic research, can provide guidance and drive innovative solutions to key RWE issues, such as how to:

- **Articulate a well-defined research question**
- **Identify the optimal study design(s), including those that support causal inference**
- **Identify RWD sources that are "Fit for Purpose"**
- **Design and implement protocols and/or analytic plans for RWD epidemiologic studies, including analysis for causal inference**
- **Enumerate appropriate data extraction procedures and validate algorithms for measurement of exposure, outcomes and relevant covariates, including accurate linkage of data sources as needed**
- **Use external control groups derived from RWD for single-arm trials and other studies**
- **Evaluate representativeness and/or generalizability of the RWE or describe relevant effect modification**
- **Quantify impact of confounding and other biases on interpretation of RWE using appropriate design and statistical techniques**
- **Interpret results of RWD epidemiologic studies in light of limitations and the totality of evidence**
- **Determine to what extent RWE could constitute "evidentiary standards" in submissions for regulatory and HTA agencies**
- **Establish Quality Assurance and Quality Control techniques for RWD sources, particularly for studies intended for regulatory purposes**

Future Directions

As the field of RWE evolves, **ISPE's vision is to continue to emphasize and define the primary importance of scientifically sound data sources, design and measurement standards, and analysis, in both non-randomized/observational and randomized studies.** Simultaneously, ISPE





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seeks to incorporate novel data sources and methods (e.g. patient generated health data) as well as newer innovative analytical technologies (e.g. artificial intelligence, natural language processing) in pharmacoepidemiological research. ISPE encourages the use of RWE, including incorporation of large, publicly funded pRCTs set in routine clinical practice, to help better inform on the comparative effectiveness and safety of medicines and other health interventions.

ISPE leads and drives exciting new developments in RWE via the breadth of experience and expertise in epidemiologic research of its members, and seeks to collaborate with key stakeholders to further the use and science of RWE. ISPE supports development of best practices and standards in the field and encourages its members to partner with relevant internal and external stakeholders through public forums to provide more extensive input into the development, implementation, and interpretation of RWE.

ISPE thanks the *RWE Taskforce on the ISPE Position Statement* for development of this document, which includes representatives from multiple professional sectors and regions.

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