Title

Real-world Evidence Studies Require Full Transparency to Ensure Appropriate Interpretation of Results

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Text

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In the midst of the COVID-19 pandemic, there is a global need for high-quality and rapid-turnaround clinical evidence. We are concerned by the damage caused by the recent publication and subsequent retractions of high-profile real-world evidence (RWE) studies in *The Lancet*[1] and *New England Journal of Medicine* (NEJM)[2]. Unfortunately, these were not the only papers published in top-tier journals during this pandemic with obvious and considerable methodological shortcomings.[3-6] Retracting flawed and unverifiable work is a critically important scientific responsibility; yet, when it happens, it raises distrust in the scientific, review, and editorial processes for medical research.

On behalf of the International Society for Pharmacoepidemiology (ISPE) RWE Task Force and the RWE Transparency Initiative led by ISPOR - The Professional Society for Health Economics and Outcomes Research, two professional organizations with more than 30 years dedicated to transparency, reproducibility and robustness of RWE research, we highlight to the research community that rigorous and valid RWE studies can, have, and will continue to be conducted by highly-trained investigators well-versed in methods for secondary analysis of routinely collected healthcare data. The high-profile retractions of these studies with serious validity concerns underscore the need to take action to avoid similar situations in the future.

Most real-world data are not originally collected for research purposes. They are context-dependent, require data validation, and are complex to use appropriately for research. Fitness of data for the research question along with numerous study design and analysis parameters must be considered and pre-specified when evaluating a hypothesis to ensure valid, robust, and interpretable results. Clear and unambiguous reporting about both RWE study conduct as well as quality of underlying data is essential to differentiate high-quality studies that can help inform healthcare decision making from low-quality studies whose findings should be disregarded.[7-9]

Both ISPE and ISPOR have actively developed guidance for RWE studies.[10-15] Best practices include pre-specification of details of the study design and analysis plan, documentation of deviation (with rationale) from the initial plan, and accountability for reproducible research. Numerous public repositories exist for the registration of RWE protocols for future inspection, including the EU PAS Register, clinicaltrials.gov, and HSRProj.[16] When a new data source is utilized for RWE studies, there should be public documentation of the robustness and quality of the overarching source database and characteristics of data elements.[17] Data provenance, including details of data transformation and cleaning, both before and during the study implementation, should be described with the study results.[18]

We note that the papers using Surgisphere[1,2] data were problematic on many levels and laud decisions to retract these papers in the absence of adequate transparency to evaluate reproducibility or robustness of findings. Nevertheless, the lack of co-authors trained in the methodology employed, absence of pre-specified protocols, inability to verify data quality, curation practices, or share analytic code should have prompted further scrutiny from RWE expert reviewers prior to publication.

These instances of publication and retraction reinforce the need for conduct, review and reporting of RWE research using standards agreed upon by professional societies dedicated to RWE. Sound knowledge of how to construct and conduct rigorous, high quality RWE studies is imperative. Such research is only as good as the underlying data and study design upon which inferences are drawn. Unfortunately, the prevalence of major design flaws in RWE studies remains troublingly high, even though naive errors in temporality and other design choices leading to biased results have been recognized for decades by pharmacoepidemiologists and outcome researchers.[19,20]

There is opportunity for experts from organizations like ISPE and ISPOR to work with journal editors and the wider medical research community, to highlight good practices in RWE research.[21] We welcome the opportunity to collaborate and assist in relevant training for the next generation of clinical researchers. We commit to join forces and play a major role in conducting, peer-reviewing, and providing transparency of RWE research.

RWE is critical to informing decision-making regarding the safety and effectiveness of medical interventions within actual clinical practice around the world. This recent experience, while a

setback, is not representative of the power and utility of RWE. As international organizations, we commit to do the work needed to build trust in the utility of RWE for researchers, clinicians, regulators, and patients.

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