Qeios

Peer Review

# Review of: "The Unregulated Majority: Who Ensures Quality in Non-HTA Real-World Studies?"

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The commentary focused on an important topic of how RWE used in non-regulatory submission studies not vigorously conducted can generate erroneous and misleading information that could potentially bias physicians or other health care workers regarding their perceptions of the effectiveness and safety of drugs evaluated. While the commentary raises legitimate concerns regarding methodological oversights and inappropriate promotional practices, it is important to recognize that the commentary tends to overgeneralize, implying that such improper behaviours are pervasive among most companies producing RWE publications.

The proposed framework offers some clear and pragmatic guidance for non-submission RWE generation. In particular, it emphasizes the need for the enhancement of specific skill sets within organizations. These measures collectively represent a positive step towards strengthening the overall quality of research and evidence generation in the field.

Despite these strengths, the framework does not include a discussion on enforcement. One option may be a robust monitoring and regulatory mechanism. A non-company affiliated governance committee set up to review and critique RWE publications/presentations to ensure adherence to published standards should be considered in the discussion.

Detailed comments:

It is inaccurate to claim that most studies are disseminated without any formal oversight. In the United States, the FDA oversees the sharing of publications with health care professionals through FDAMA regulations, while in Canada, PAAB serves a similar regulatory function to ensure appropriate

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communication. Companies face substantial penalties if they fail to comply with these standards. Please rewrite the last paragraph.

The Blind Spot:

First paragraph: please define ‘Low impact’ journals, ones with low impact factors; provide a number or a range.

1. Protocol shortcut: Many non-submission studies – maybe an over-extraction, please quantify.
2. Add “with confidence intervals” after causal inferences.
3. Add other methodological issues such as data quality and data governance, selection bias, intercurrent confounders, immortal time bias... all need to be considered as part of the analysis of RWE.
4. Define how to quantitate weak review. It is
5. It is considered acceptable for physicians to increase prescriptions while participating in a clinical trial, as ongoing involvement allows them to better understand the benefit-risk profile of a medication and determine optimal administration practices. Poor-quality RWE is unlikely to significantly drive this behavior, since clinical decision-making in this context is typically shaped by firsthand experience and robust evidence. Additionally, highlighting disease etiology and burden to educate physicians prior to the launch of a medication is also appropriate, as it ensures clinicians are well-informed about the underlying need for new therapies.

In many instances, RWE plays a crucial role in defining the natural history of diseases and in providing comprehensive background information that supports treatment decisions. This context can enhance the clinical understanding necessary for introducing new medications and help ensure that their use is both evidence-based and aligned with patient needs.

1. Please clarify “local level.” This may be jargon used by companies for subsidiaries or affiliates but might confuse readers.
2. The two examples provided regarding diabetic and oncology patients did not clearly illustrate how RWE use produces fraudulent analysis.

Why it matters:

The commentary discusses how non-submission RWE data has the potential to mislead health care professionals regarding the efficacy and risks of medications, potentially resulting in inappropriate

treatments. While such risks are genuine and merit careful consideration, it is also important to recognize that many rigorously conducted RWE studies have contributed valuable insights, such as clarifying disease natural histories and providing essential background on treatment patterns. To present a more balanced perspective, the commentary should also highlight the positive impact and utility of non-submission RWE studies in enhancing clinical understanding and supporting evidence-based decision-making.

Proposed framework

The three proposed bullet points represent important steps towards ensuring that RWE is conducted with scientific rigor and supports evidence-based practice. In addition to these, analytical transparency should encompass elements such as data quality, data governance, database transparency, and the use of a robust statistical analysis plan (akin to an SAP) to ensure that outcomes generated from real-world data are reliable and reproducible.

However, a key element still missing is the establishment of a comprehensive monitoring structure designed to minimize the dissemination of low-quality RWE and reduce its potential influence on health care professionals. To further mitigate the risk of harm, it is also essential to educate end users—including clinicians and decision-makers—on how to critically appraise RWE. This education should empower them to distinguish between high-quality, actionable evidence and studies of questionable validity, supporting the adoption of only genuine and practice-changing findings.

## Declarations

**Potential competing interests:** No potential competing interests to declare.