Is Real-World Evidence Needed in Comparative Effectiveness Research? Yes, But…

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Real-world evidence (RWE) is increasingly recognized as a key source of information and insight in conducting comparative effectiveness research (CER). This is particularly true in the context of demonstrating product value through comparative effectiveness assessment (CEA) involved in health technology assessment (HTA). However, the disparate nature of RWE coupled with the lack of definitive guidance on its use means there can be confusion, scepticism, or even distrust about its inclusion in attempts to compare treatments outside the setting of head-to-head interventional studies. This article discusses these concerns and how they might be addressed.

Why RWE?

CER is an analytical process to demonstrate "the extent to which an intervention does more good than when compared to one or more intervention alternatives for achieving the desired results and when provided under routine setting of health care practice"[1] (i.e., in the real-world setting). The main drivers for the use of RWE in such analyses are circumstances in which randomized controlled trials (RCTs) are not feasible or have limitations that leave key gaps in knowledge. Such data, in theory, can either supplement, or compensate for the absence of, relevant RCTs and may thereby provide a broader perspective of a product's effects. Specifically, while RCTs seek to answer the question "Can this product work in a highly selective, relatively homogeneous population?," RWE might help provide the answer to "Does this product work for a heterogeneous group of patients that would be found in a typical everyday clinical setting?" *(Figure 1)*.

However, deciding whether, where, and how to employ RWE in this way is complicated by the lack of definitive conceptual frameworks, accepted guidance, and collective, longstanding experience associated with the generation and use of RCT data. Indeed, there is even a lack of standardization and agreement on what is the "right" term to define data that captures patients' experiences of receiving a technology under real-life conditions and what evidence should be included under this umbrella. The terms RWE, real-world data (RWD), and "big data" are often used interchangeably to describe everything from patient-level data collected in electronic health records (EHRs) from insurers or governmental health programs, to patient registries, to surveys and information gathered through health "apps" and other connected devices. Against this background, it is not surprising that even those who recognize the potential benefits of RWE in CER may be daunted by the practicalities of their use.

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What are the Main Challenges for RWE in CER?

The biggest obstacles in efforts to use RWE in CER relate to developing a valid and reliable process for data collection and analysis that will provide unbiased estimates of a technology's effectiveness compared to standard clinical care. Meeting this objective is clearly paramount where data on the product will be scrutinized by HTA bodies or payers seeking to decide whether reimbursement is justified.

Until recently, however, a lack of trust related to inherent limitations of RWE has hindered the uptake of such data into HTA/payer decision-making. These doubts specifically include worries about the quality of both the sources and collection of RWE, patient selection processes, and publication bias in reporting of the data. Consequently, CER continues to be heavily based on the methodological interpretation of RCT evidence and evaluating the level of "uncertainty" produced by that type of evidence.[2-4] In this context, use of RWE to demonstrate a technology's value in reimbursement processes has been restricted to supplementing sparse RCT evidence or providing information on epidemiology and burden of disease (humanistic and economic) for pharmacoeconomic analysis.

How Can the Challenges be Overcome?

Ways of increasing the validity of RWE in CER include appropriate choices between potential data sources, transparency in data collection, and the use of available methods for addressing limitations related to the lack of randomization of treatment allocation. The following diagram summarizes the most widely proposed approaches that can be considered by investigators and drug companies when RWE is needed to help define a technology's relative effectiveness *(Figure 2)*. These

Figure 1. Lack of Trust and Limited RWE in Initial Reimbursement Decisions

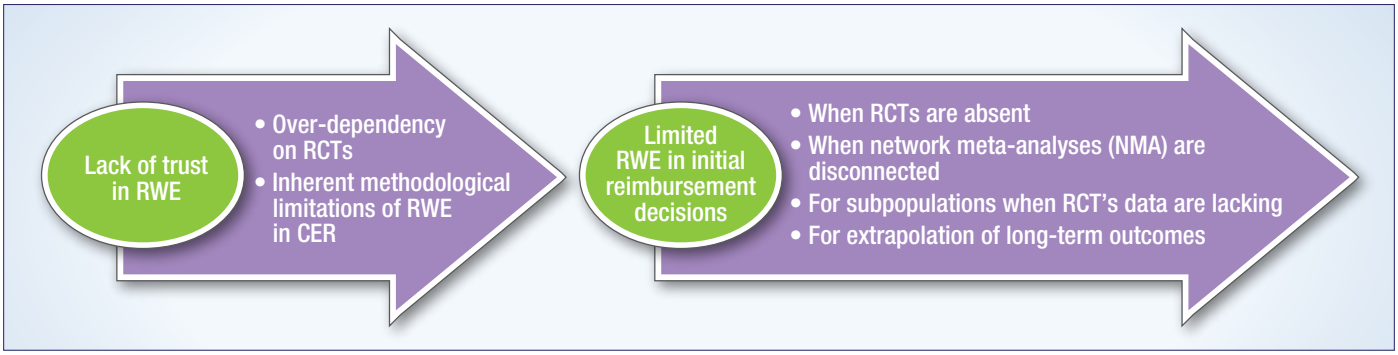
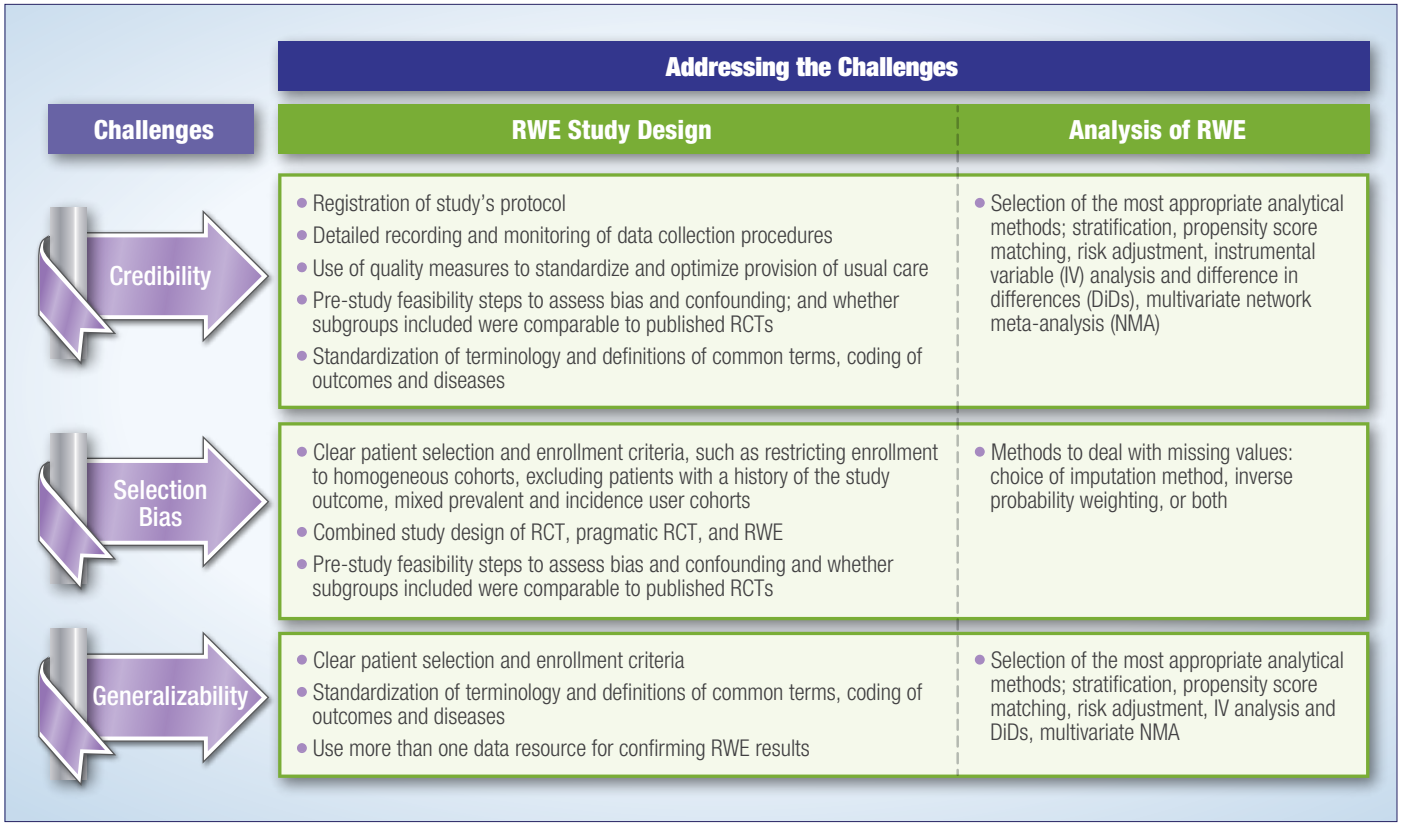
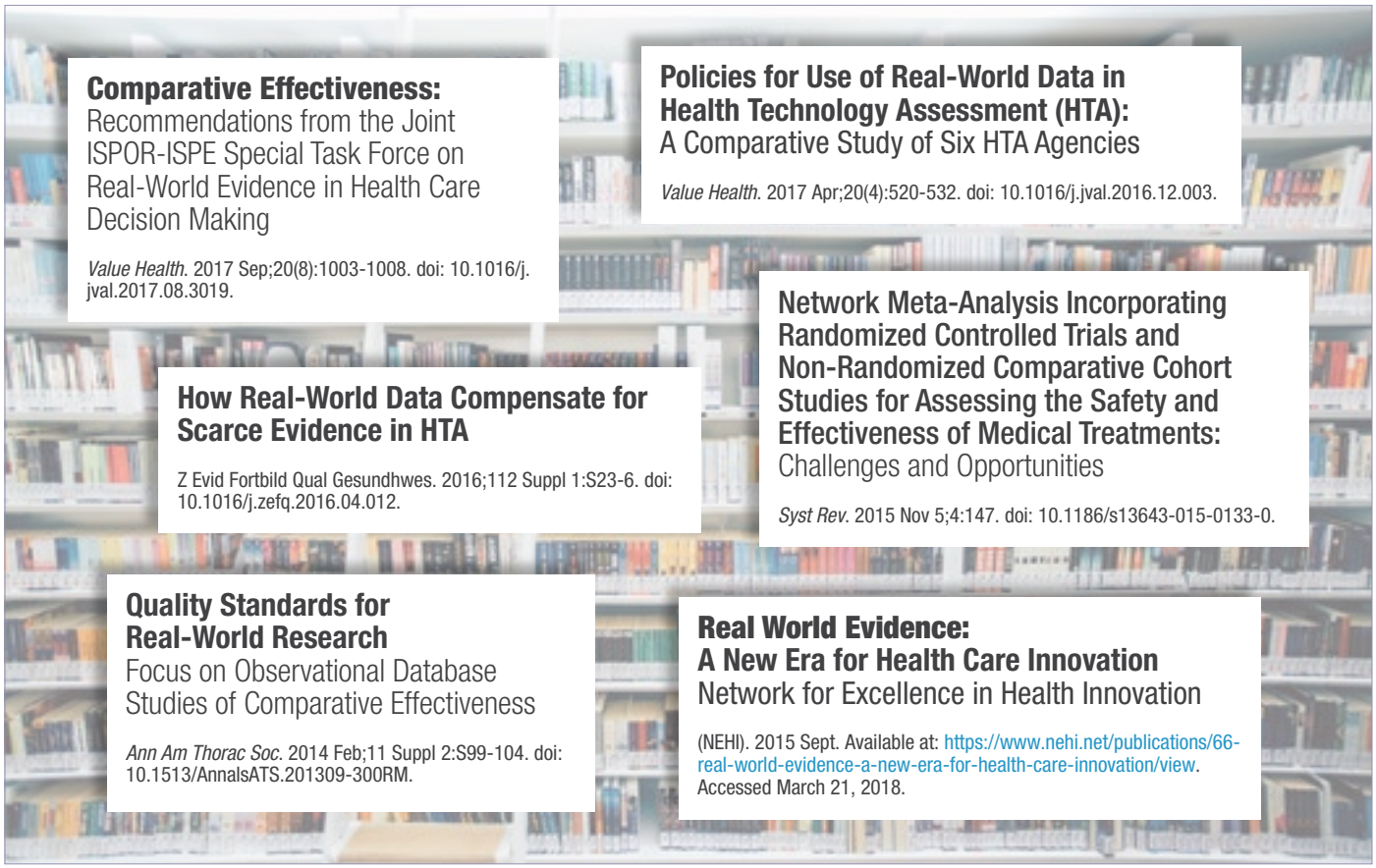


Figure 2. How Can the Challenges be Overcome?



Samples of the Proliferation of RWE for CER Publications in Recent Years



solutions target the three main challenges related to the interpretation of RWE findings in CER: selection bias; credibility of the data-collection process; and, generalizability of findings to the population for whom the technology is intended.

What are the Current Place and Potential of RWE in CER for Reimbursement Decision-Making?

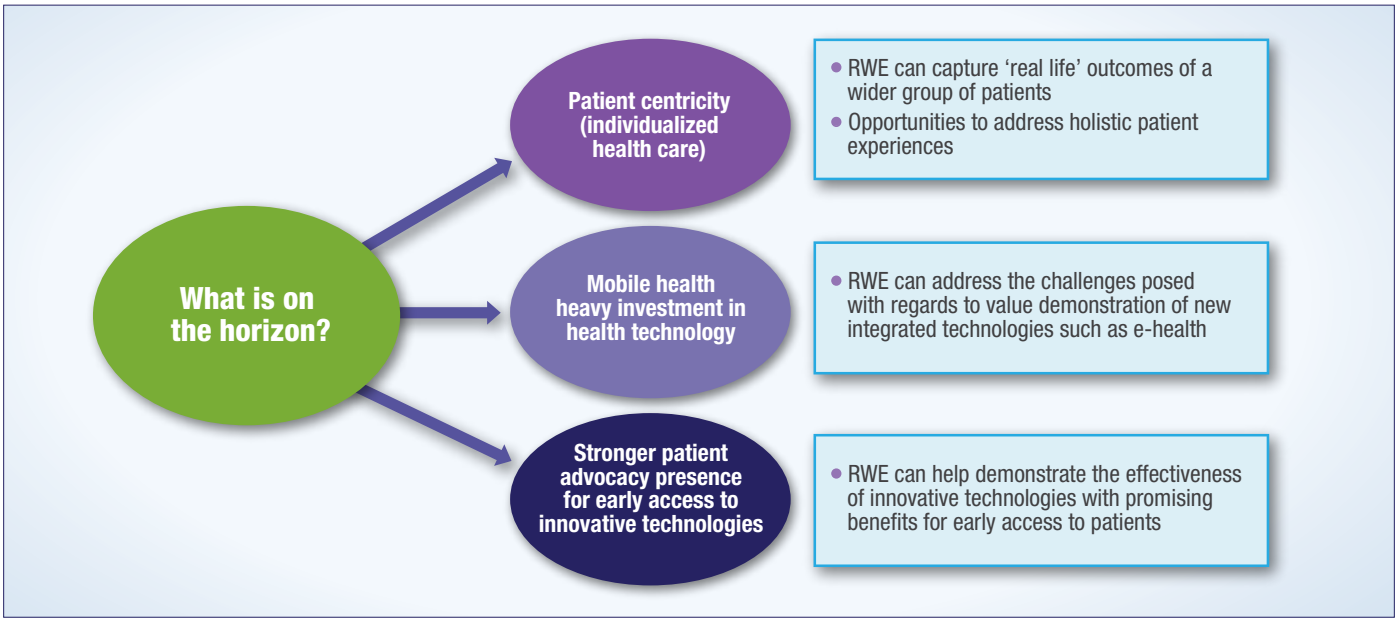
It is important to note that the potential for integrating RWE in health care decision-making is not new. For example, the first International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Real-World Data Task Force Report, published in 2007, proposed a framework for use of RWE in health coverage and payment decisions and emphasized the role of estimates of effectiveness rather than efficacy in a variety of typical practice settings.[5]

What has Changed in Recent Years to Increase the Spotlight on RWE?

Globally, there is a movement to capitalize on the potential for RWE in CER.

- In Europe, the Innovative Medicines Initiative GetReal Consortium (IMI-GetReal) has been a major influence in promoting close collaboration between different stakeholders (including academics, policy makers, and pharmaceutical companies) to investigate policies and methodologies for the collection and use of RWE in drug development and assessment. Furthermore, the RWE-navigator (https://rwe-navigator.eu/) – an output of this initiative – now serves as an educational and guidance tool to enable users to understand issues around demonstrating relative effectiveness of a new technology, therefore enabling the identification of the best study designs or analytical approaches to address these issues.
- In the U.S., the 21st Century Cures Act[6] stated the need for the Food and Drug Administration to develop a regulatory framework to evaluate RWE potential to support approval of new indications for approved drugs or satisfy post-approval study requirements.
- Recent changes in the market access landscape, with shifts in pharma health economic and outcomes research (HEOR) activities and HTA requirements, have facilitated the increased role for RWE in CER. In addition, the requirement to incorporate RWE into CER is likely to grow with the transformative possibilities of mobile health,[7] the changes in the conceptualization and operationalization of health care (including greater emphasis on individualized management and the patient voice in decision-making), and the push for earlier introduction of innovative technologies into the market[8,9] (such as Early Access Management Schemes) *(Figure 3)*.

Figure 3. The Increasing Role of RWE



Conclusion

Although the assessment of product value will probably still be largely determined by efficacy in "hard" clinical and/or cost-effectiveness outcomes such as mortality and quality-adjusted life years (QALYS), the current landscape clearly indicates a growing interest in using RWE throughout the drug development and assessment process. New trends in health technology assessment are expected to place a higher value on the use of RWE in CER and/or in supporting technology in initial reimbursement or post-marketing assessments. Once seen as the lesser to so-called "gold standard" evidence, RWE increasingly will be seen as a must-have in CER. ■

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REFERENCES

1. REES France Health Evaluation Network. High Level Pharmaceutical Forum 2005-2008 Final Report. Available at: http://www.rees-france.com/en/IMG/pdf/2008_High_level_Pharma_forum__en_final_report.pdf. Accessed March 28, 2018.
2. Freemantle N, Strack T. Real-World Effectiveness of New Medicines Should be Evaluated by Appropriately Designed Clinical Trials. *J Clin Epidemiol.* 2010 Oct;63(10):1053-1058. doi: 10.1016/j.jclinepi.2009.07.013
3. Eichler HG, Abadie E, Breckenridge A, et al. Bridging the Efficacy-Effectiveness Gap: A Regulator's Perspective on Addressing Variability of Drug Response. *Nat Rev Drug Discov.* 2011 Jul 1;10(7):495-506. doi: 10.1038/nrd3501.
4. Nordon C, Karcher H, Groenwold RH, et al. The "Efficacy-Effectiveness Gap": Historical Background and Current Conceptualization. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2016;19(1):75-81.
5. Garrison LP Jr, Neumann PJ, Erickson P, Marshall D, Mullins CD. Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report. *Value Health.* 2007 Sep-Oct;10(5):326-35.
6. H.R.34 - 21st Century Cures Act. 2016. Public Law 114-255, 114th Congress, December 13, 2016. Available at: https://www.congress.gov/114/plaws/publ255/PLAW-114publ255.pdf. Accessed March 19, 2018.
7. Atreja A, Bates D, Clancy D, Daniel G, et al. Duke Margolis Center for Health Policy. Mobilizing mHealth Innovation for Real-World Evidence Generation. Available at: https://healthpolicy.duke.edu/sites/default/files/atoms/files/mobilizing_mhealth_innovation_for_real-world_evidence_generation.pdf. Accessed March 21, 2018.
8. National Institute for Health and Care Excellence (NICE). Cancer Drugs Fund. 2016. Available at: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/cancer-drugs-fund. Accessed March 21, 2018.
9. O'Connor D. Medicines and Healthcare Products Regulatory Agency. Early Access to Medicines Scheme (EAMS): Safe and Timely Access to Medicines for Patients (STAMP). May 2015. Available at: https://ec.europa.eu/health/sites/health/files/files/committee/stamp/2015-05_stamp2/5.pdf. Accessed March 21, 2018.