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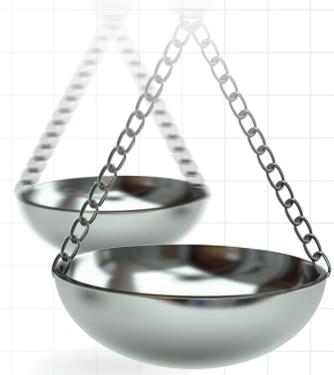

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R WE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment

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Highlighting the latest developments in both real-world evidence as it relates to health technology assessment and acceptance of real-world evidence by health technology assessment agencies.

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Real-world evidence (RWE) has experienced an explosion of interest within the last decade, as a result of the availability of more data sources and a plethora of applications across a product lifecycle [1]. Given the breadth of use cases of RWE, it is no surprise that it is sometimes considered as a valuable tool in the health technology assessment (HTA) process. Barriers to the widespread adoption and acceptance of RWE by HTA agencies do however remain [2]. The focus of this bi-monthly series is therefore to highlight developments in both RWE as it relates to HTA and acceptance of RWE by HTA agencies, and we kick off the series discussing news of interest for each.

RWE initiative relating to HTA: RCT-DUPLICATE

A recent study from the randomized controlled trial (RCT)-DUPLICATE initiative reported the findings from the first ten trial emulations evaluating cardiovascular outcomes of antidiabetic or antiplatelet medications using RWD from three US healthcare claims data sources [3]. Patients were selected according to corresponding RCT inclusion/exclusion criteria, and end points similarly matched in claims data. Analyses were prespecified and a protocol registered before study initiation. Propensity score matching was used to balance *a priori* defined confounders. In six of the ten studies, 'regulatory agreement' was achieved, meaning that the RWE study was able to replicate the direction and significance of the RCT finding and in nine of the ten studies, regulatory or estimate agreement criteria was fulfilled, the latter of which meaning the RWE hazard ratio landed within the 95% CI of the RCT hazard ratio. Taken together this study demonstrates that in certain circumstances RWE may be able to support causal conclusions, providing options when RCTs may not be feasible.

Given the body of evidence presented to regulators typically forms the core of that subsequently presented to HTA bodies and payers, it is vital that those involved in HTA/market access remain aware of these developments and proactively consider any potential impact for HTA. The outcomes from Franklin *et al.*, however, may not translate directly into outcomes that would be important for HTA decisions [3]. For example, the measure of 'regulatory agreement' may not translate into a similar concept of 'HTA agreement', as HTA bodies are more concerned with the magnitude of effect and implications for cost–effectiveness estimates rather than simply the existence and direction of an effect.

Nonetheless, RCTs conducted in 'ideal and controlled situations' and effectiveness estimates from RWE collected in the 'real-world' may be interpreted as answering different research questions and; therefore, we would not necessarily expect to obtain the same estimates, even after aligning inclusion/exclusion criteria and adjusting for pre-exposure confounders. While perhaps not the case for regulators, the research question being answered by the real-world study is actually the question of most interest to HTA bodies, albeit in practice the potential for bias limits the extent to which RWE can be used to drive HTA decision making. Therefore initiatives like RCT DUPLICATE

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provide more information as to when HTAs can rely on RWE for decision making around effectiveness. To this end, Franklin *et al.* replicated regulatory processes by registering a protocol before analyzing the study outcomes. This is not a strict requirement for analyses conducted for HTA purposes (e.g., indirect treatment comparisons) but could be part of the guidance that HTAs could provide outlining what types of RWE they will consider in their decision making, aligned with recent RWE transparency initiatives [4,5].

HTA acceptance of RWE: G-BA & Zolgensma

Evidence available at the time of reimbursement decision making for rare disease therapeutics may have a higher degree of uncertainty; studies may be considered too short to assess long-term outcomes, lacking in important patient relevant outcomes and/or feature no standard of care comparison. In 2020, the Federal Joint Committee (G-BA) in Germany passed legislation with the remit to mandate the collection of post-launch RWE for advanced therapy medicinal products. The G-BA subsequently commissioned the Institute for Quality and Efficacy in HealthCare (IQWiG) to develop scientific concepts for the generation of routine practice data and their analysis for benefit assessment of drugs in Germany, particularly with regards to quantifying the added benefit of a new drug. IQWiG concluded that high-quality registries are most likely to help inform benefit assessment, while other RWE sources, such as electronic medical records and claims data, were less promising due to concerns over insufficient data quality and completeness [6]. Novartis' gene therapy for spinal muscular atrophy (SMA), Zolgensma, was the first drug to have post-approval RWE mandated by the G-BA in February 2021. In line with the recommendations of the IQWiG report referred to above, Novartis will have to perform a registry based study to include up to 500 children with presymptomatic SMA and SMA type 1 and type 2, and effectiveness compared with Biogen's Spinraza.

While German authorities have long been viewed as reluctant to use RWE to support decision making regarding reimbursement of new drugs, these recent advancements demonstrate a commitment to utilzing RWE, particularly in situations where there is significant unmet need and obvious barriers to the generation of head-to-head comparative evidence. Their focus on registry studies may; however, appear to some to be overly restrictive, particularly in light of the RCT-DUPLICATE results noted above.

As we look into the future, it will be interesting to see if the approach taken in the case of Zolgensma becomes the new norm in Germany for rare diseases. If so, a few considerations arise. While SMA benefits from the availability of high quality registries, this may not always be the case. In addition, if the disease is of such rarity that there would be insufficient numbers of patients in a single country to provide a robust answer on real world effectiveness, data from other countries may need to be considered. The German authorities should be commended for beginning to map out a pathway for the use of RWE in their assessments to enable patient access to medicines, and we will be following with interest to see how this guidance develops in the future.

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