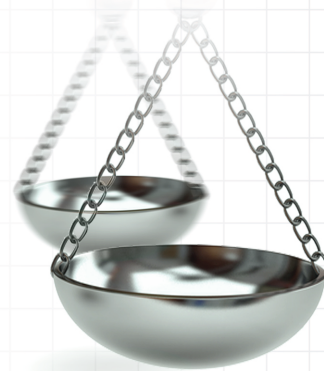




RWE ready for reimbursement? A round up of developments in real-world evidence relating to health technology assessment: part 13

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In this latest update we highlight a report from the European Medicines Agency on their use of real-world evidence (RWE) in decision making, RWE reporting guidance from the Canadian Agency for Drugs and Technologies in Health and highlight some new data demonstrating the value medicines for spinal muscular atrophy have brought patients.

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The European Medicines Agency (EMA) has been on a journey of discovery to understand how real-world evidence (RWE) can complement data from clinical trials for regulatory decision making. While the use of RWE is well established for the post-marketing safety surveillance of medicines, the use of RWE by regulators to address evidence gaps earlier in the product lifecycle (such as clinical effectiveness), is at a much earlier stage of evolution.

In 2021, a pilot was carried out with the Pharmacovigilance Risk Assessment Committee (PRAC) to test a framework for conducting 'in-house' RWE studies to help PRAC evaluations, largely using data from electronic health records (EHR) available to the EMA at that time. The pilot concluded with recommendations to optimize RWE support for the PRAC and to broaden support to other committees. Since the completion of the pilot, the EMA has been routinely offering RWE support to the PRAC and has been exploring the potential for RWE to assist other Committees and Working Parties. In addition to access to several, mostly primary care focused, health research data sources, in 2022, the Data Analytics and Real World Interrogation Network (DARWIN EU) was born. This is a European federated network of real-world data (RWD), somewhat analogous to the FDA's Sentinel initiative, and included ten data partners in its first year.

The EMA has now published a report sharing early learnings from these RWE initiatives, encapsulating nearly a year and a half of experience [1]. During this time, 61 potential RWD research opportunities were identified to aid regulatory decision-making. Out of these, 36 studies (59%) were deemed feasible, while 19 (31%) were found unfeasible and six were pending further discussion. Among the feasible studies, 27 (75%) have been completed, three are in progress, and six (17%) were proposed to rapporteurs/lead member states but were not asked by them to be executed (RWD studies can either be requested by committees or suggested by the EMA RWE team). The majority of the research ideas were targeted toward producing evidence about the safety of medicines, and, notably none of these focused on treatment effectiveness. The most common reasons why studies were infeasible will be very familiar to researchers in this field: lack of information about exposure to the medicine of interest in the available data sources (often because these were not prescribed in primary care), or inability to accurately identify the relevant outcomes [2]. For 18 completed studies, surveys were conducted to assess their impact. Most respondents (63%) affirmed that the study results were useful: while results from ten studies were incorporated into assessment reports,

in two cases the results were found to be helpful but not vital for the final decision. In three instances, the studies weren't factored into decision-making: for two this was because of data issues (one because patients in secondary care would be missed from primary care databases, and the other because a code list may have been too broad). In the third instance, while a study's usefulness was acknowledged, case reports and clinical trial data were deemed more pertinent. Studies undertaken in-house by the EMA were quick to generate RWE to aid decisions when appropriate data sources were available, taking an average of 56 days. However studies using DARWIN EU took on average 215 days, though it is hoped the network will evolve over time to deliver study results more swiftly.

Overall, the report underscores the utility of RWE in supporting regulatory decision-making, while also highlighting the challenges and considerations in its use. As noted in the report, access to diverse (different countries to represent all of the EU) and detailed data sources (covering many indications including rare disease, and including all parts of the patient care pathway), is crucial but very challenging. Primary care data alone will never fully meet the RWD needs of regulatory decision making, and access to hospital EHRs, registries and specialist therapy area data sources will be essential. The call for greater data availability may not come as a surprise, being the subject of attention from many stakeholders over recent years [3,4]. Hopefully the weight of EMA advocacy can accelerate data sharing efforts and the EMA has the opportunity to become an active stakeholder in supporting the growth of the RWD ecosystem. The EMA could also look ahead to the likely future horizon of regulatory submissions to try and anticipate the required RWD and reduce the risk that the right data is not available when it is needed.

The EMA could also be more open to using data from other regions, similar to the stance taken by NICE, whose RWE framework recognizes that the choice of data source may involve a trade-off between locality and data content and quality [5]. Additionally of note is the fact that no study to date has investigated treatment effectiveness, the study type that generally has the lowest level of acceptability by decision makers [6]. While the internal use of RWE by the EMA may not be directly relevant to health technology assessment (HTA), evidence used and decisions made by regulators typically starts the ball rolling for market access activities, and therefore following future developments in how the EMA utilizes RWE is warranted. It remains to be seen whether HTA agencies will also begin to perform data analyses internally to support reimbursement discussions.

On the topic of reimbursement discussions, the Canadian Agency for Drugs and Technologies in Health (CADTH) recently released guidance for those undertaking and submitting RWE studies for regulatory and HTA decision making in Canada [7]. The guidance states that it also provides decision makers with information required to appraise studies, but does not provide advice as to when or why RWE should be used. The guidance delves into the specifics of reporting of all aspects of RWE studies, starting with the formulation of research questions and study design through to reporting study findings and its limitations. For study design, it recommends using the population, intervention, comparator, outcome, timing and setting (PICOTS) template to frame the research question, with a review of the literature to support the study rationale. Studies attempting to address a causal research question are advised to use a target trial emulation approach, and pre-registration of protocols (potentially developed using the HARPER template [8,9]) is recommended, especially when a study is investigating treatment effectiveness. The guidelines also recommend that protocols should be discussed early with regulators and HTA agencies if the study is to be used in a submission. Data sources (and variables) used must be described in detail, and non-Canadian sources are acceptable but the transferability to a Canadian context must be outlined. Subjects included in studies should be described in terms of their diversity (e.g., age, sex) and there should be discussion as to how historically underrepresented groups in research are included. The potential for bias should be described, as well as ways in which this was attempted to be minimized, along with their expected impact on outcomes. Similarly the selection of potential confounders should be reported, and a causal diagram is proposed to be beneficial to do this. Negative outcomes, sensitivity analyses for assumptions, and quantitative bias analysis [10,11] should all be considered for use to strengthen study findings. Statistical code used should ideally be shared.

In summary, the guidance from CADTH is comprehensive, especially emphasizing the importance of transparency, detail, and rigor in all aspects of RWE reporting. The guidelines pick up many of the same themes and recommendations as NICE has done for its RWE framework and should help to support more of a shared understanding across HTA bodies about "what good RWE looks like". The non-prescriptive nature of the guidance is useful. However, the trade-off with this flexibility is that it does leave significant room open for researcher interpretation, which then leaves the door open for debate as to whether investigators followed the best approach, and ultimately to the RWE generated by the study not being accepted by key stakeholders. It will be interesting to observe how RWE is appraised by CADTH in the future when manufacturers submit RWE to them following this guidance.

To conclude the 13th part of this series, we review some new data investigating the population level benefits of treatment for spinal muscular atrophy (SMA) [10]. Over recent years, the pricing of new treatments for SMA has drawn significant attention, and therefore the real-world effectiveness of these treatments is of considerable interest. Historically, only 8% of babies born with SMA type 1 (SMA1) reach 20 months of age without needing permanent ventilatory support. Data from the SMA REACH UK database reveals that 73% of children with SMA1 in the UK now survive beyond 2 years, a dramatic improvement attributed to the three SMA medicines that have been reimbursed: spinraza, zolgensma and evrysdi. Words perhaps cannot describe the life-changing impact these medicines have had for parents of children with SMA, and really does demonstrate that for medicines, discussions should be around value, not price [12].

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