Regulatory vs HTA divergences- Can the Real-world Evidence (RWE) be the connecting bridge?

RWD136

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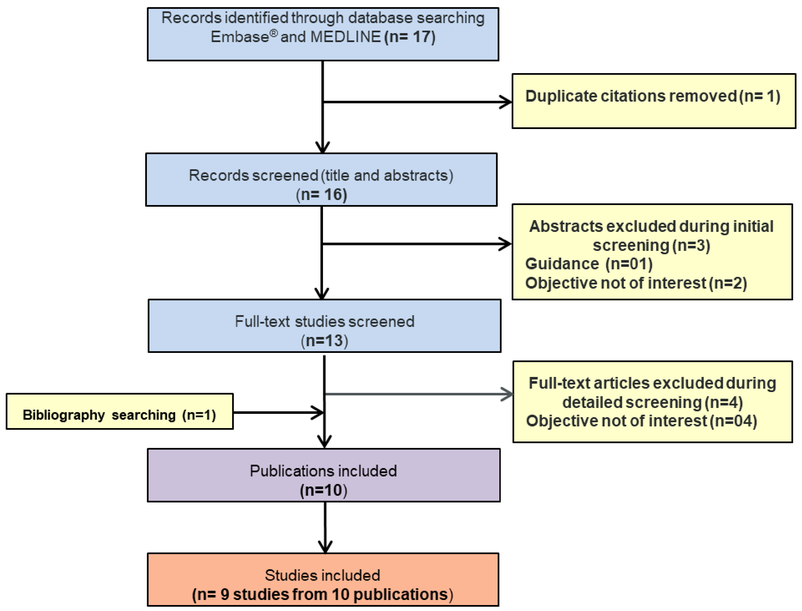
Background

- Patient access to new medicines requires regulatory approval from country-specific regulatory and reimbursement HTA bodies.
- Regulatory agencies evaluates new intervention from risk benefit perspective whereas HTA bodies analyze it through a prism of relative effectiveness and budgetary considerations.
- Divergences between these two bodies can lead to delayed patient access to new interventions thereby leading to poorer health outcomes, decreased quality of life, and increased morbidity or mortality rates
- Between March 2000-2018, among all new medicines approved by European Medicines Agency (EMA) only 56% were recommended by the UK's National Institute for Health and Care Excellence (NICE).
- The objective of this research was to identify reasons of divergence and understand if greater use and analyses of RWE may address this gap, leading to positive HTA outcomes.

Methods

- Systematic search of electronic databases MEDLINE®, EMBASE® was undertaken using keywords "HTA", "regulatory, divergences" and "RWE/D" since database inception (Figure 1)

Figure 1: Flow of studies



Results

- A total of 9 articles were retrieved. These publications assessed interactions, synergies and divergences among regulatory and payer stakeholders.
- All of these were recent publications (post 2016), indicating towards the growing interest in developing common or single development plan for newer therapies
- There was alignment on majority of the evidence requirements between regulatory and HTA bodies. However, few key divergences were observed
- The most important differences were the choice of primary endpoint, comparator, and use of surrogate outcomes (Figure 2). It was observed that HTA bodies preferred active comparators over placebo, emphasized more value in demonstrating long-term benefits, and were more critical on the use of surrogate outcomes. These could be the reasons due to which a product achieving successful market authorization was not able to achieve same success on the reimbursement front.
- These divergences could be addressed by using RWE, integrated throughout product development lifecycle. RWE can be used to support endpoint selection and protocol optimization that may align with HTA expectations. Generating data on additional outcomes and long-term data on primary outcomes (through post-authorization studies using RWD sources) can provide relative efficacy data (through RWD derived external controls arm) which is increasingly expected by HTA bodies.
- However, regulatory and HTA bodies share concerns about quality of RWE. To streamline and align on acceptability of RWE, many regulatory and HTA bodies have developed RWE frameworks, guidance on data quality and study methodology. Duke-Margolis Center for Health Policy recommended "totality of evidence" approach to generating evidence that is informative both for regulators and payers. Early engagement with regulatory and HTA agencies on use of RWE can help addressing reimbursement challenges.
- As the evidence was limited to articles published in the English language, this may limit the generalizability of the findings. We presented in this research key divergences, however there may be other less important differences between regulatory and HTA bodies contributing to the misalignment.

Conclusions

- This study highlights key divergences between regulators and HTA bodies regarding clinical evidence requirements on primary endpoint, choice of comparator and use of surrogate outcomes. RWE has great potential for building a robust data ecosystem equipped to support both regulatory and payer decision making and can act a bridge to address these divergences.
- Therefore, establishing early engagement and fostering collaboration between industry, regulatory agencies, and HTA bodies, along with proactive discussions on proper use of RWE to address their feedback, can effectively reduce divergences and expedite patient access to new treatments.

References

- Tafuri G, Pagnini M, Moseley J, Massari M, Petavy F, Behring A, Catalan A, Gajraj E, Hedberg N, Obach M, Osipenko L. How aligned are the perspectives of EU regulators and HTA bodies? A comparative analysis of regulatory-HTA parallel scientific advice. British journal of clinical pharmacology. 2016 Oct;82(4):965-73.
- Jansen E, Hines PA, Berntgen M, Brand A. Strengthening the interface of evidence-based decision making across European regulators and health technology assessment bodies. Value in Health. 2022 Oct 1;25(10):1726-35.
- CIRS. Uncertainty in the development of new medicines. 2023 Workshop report
- Curtis LH, Sola-Morales O, Heidt J, Saunders-Hastings P, Walsh L, Casso D, Oliveria S, Mercado T, Zusterzeel R, Sobel RE, Jalbert JJ. Regulatory and HTA Considerations for Development of Real-World Data Derived External Controls. Clinical Pharmacology & Therapeutics. 2023 Aug;114(2):303-15.
- Vreman RA, Naci H, Goettsch WG, Mantel-Teeuwisse AK, Schneeweiss SG, Leufkens HG, Kesselheim AS. Decision making under uncertainty: comparing regulatory and health technology assessment reviews of medicines in the United States and Europe. Clinical Pharmacology & Therapeutics. 2020 Aug;108(2):350-7.
- Wang T, McAuslane N, Liberti L, Leufkens H, Hövels A. Building synergy between regulatory and HTA agencies beyond processes and procedures—can we effectively align the evidentiary requirements? A survey of stakeholder perceptions. Value in Health. 2018 Jun 1;21(6):707-14.
- Ofori-Asenso R, Hallgreen CE, De Bruin ML. Improving interactions between health technology assessment bodies and regulatory agencies: a systematic review and cross-sectional survey on processes, progress, outcomes, and challenges. Frontiers in Medicine. 2020 Oct 16;7:582634.
- Mahendraratnam N, Mercon K, Eckert J, Romine M, Kroetsch A, Frank K, Sherman R, Daniel G, McClellan M. Adding Real-World Evidence to a Totality of Evidence Approach for Evaluating Marketed Product Effectiveness. Duke-Margolis Center for Health Policy. 2019
- Wang T, McAuslane N, Goettsch WG, Leufkens HG, De Bruin ML. Regulatory, health technology assessment and company interactions: the current landscape and future ecosystem for drug development, review and reimbursement. International Journal of Technology Assessment in Health Care. 2023;39(1):e20.
- Grignolo A, Siu A. Improving drug development and patient access with the right people, processes, and culture: what needs to happen right now to bring better medicines to the patients who need them. Ther Innov Regul Sci. (2019) 53:398–402.

Figure 2: Key divergences identified between regulatory and HTA bodies and how RWE can help in addressing that