Lessons Learned from Successful Real-World Evidence (RWE) Studies Supporting Regulatory Drug Approvals

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OBJECTIVES:

Increasing number of NDAs and BLAs submissions have been supported by real-word evidence (RWE) for drug effectiveness. This study aims to provide lessons learned from selected successful RWE studies in recent FDA submissions.

METHODS:

Targeted literature review was performed on articles summarizing FDA approvals with RWE study from 2017 to 2021. The corresponding submission packages, FDA briefing documents and multidisciplinary reviews documents were reviewed for each approval. Cases received FDA recognition that RWE provided essential evidence in approval were summarized.

RESULTS:

Less than 10 approvals had their RWE recognized by FDA as essential. The most successful cases span wide therapeutic areas, including Lutetium Lu 177 dotatate and avelumab in oncology, pretomanid in infectious disease, cerliponase alfa in neuro disorder, etc.. FDA acknowledged the use of responses (e.g., overall response rate and duration of response) assessed by the independent review committees as oncology real-world endpoints and generally did not consider RWE using non-RECIST (Response Evaluation Criteria in Solid Tumors) criteria in solid tumors studies. Real-world survival outcomes (e.g., PFS) are not recommended unless time zero is proved to be consistent with trial. Non-oncology outcomes that are discrete or acute events have a higher acceptance rate. Factors frequently favored by FDA in RWE submissions include large effect size compared to historical threshold from RWE, the high unmet need of the disease population, improved drug toxicity profile, meaningful drug mechanism of action, well-defined real-world endpoints consistent with trials, and proper uses of statistical methods in matching baseline covariates in predefined protocols and SAPs.

CONCLUSIONS:

The number of FDA approvals with RWE as essential evidence remain limited. Study design, drug and disease situations mainly affect FDA's acceptance for RWE. Engage early with FDA in RWE study design. Statistical adjustments greatly increase the scientific validity and robustness but may not rescue all caveats in study design.