Paper RE02

Avoid Major Pitfalls When Using Real-World Evidence (RWE) in Regulatory Submissions

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ABSTRACT

The cost of bringing a medicinal product through all phases of drug development is upwards of USD $1.5 to 2.5 billion, with clinical trials making up a significant proportion of related R&D spend.[1] It's complicated and expensive. Submitting regulatory dossiers to authorities, incl. outcomes of clinical trials, increasingly requires a combination of evidence generated from harmonized data assets (RCTs) along with RWD. Access to global, row level RWD coupled with clinical evidence, usage and benefit/risk ratio from analyzing RWD is fundamental to drug development, programmatic risk reduction, commercial expansion, and patient outcomes. It is of increasing value when making submissions to regulatory authorities. SAS advanced analytics, combined with BC Platforms' data access to diverse global patient cohorts, delivers highly controlled, bespoke and fit-for-purpose data, evidence, and insights. Tapping into the combined power of secure RWD sources and analytics helps to avoid major pitfalls when using RWE in regulatory submissions.

INTRODUCTIO

Access to globally sourced and previously untapped, row level RWD is of increasing value when generating evidence to inform regulatory submissions, meeting cost and speed business challenges head on. This, coupled with the clinical evidence about the usage and potential benefits or risks of a medical product derived from the analysis of RCT data, is fundamental to drug development, programmatic risk reduction, commercial expansion prioritization, health care provision, and patient outcomes. But using RWE in clinical submissions is not without challenges. In this paper we describe 4 challenges in the use of RWE as part of regulatory submissions.

BC Platforms and SAS formed a partnership in 2022 to support the use of RWE in regulatory submissions for medicinal products—delivering powerful analytic solutions and access to diverse global patient data, combined with repeatable, modular, and easy-to-use management capabilities that provide swift and controlled data access. By tapping into the power of data and analytics, drug developers can avoid major pitfalls encountered when using RWE to make regulatory submissions for medicinal products and improve regulatory submission success.

1. START EARLY, THINK STRATEGICALLY

Focus on the overall evidence package that is required, based on RCT and RWE is key. Ideally companies would develop an integrated evidence generation plan up front. for evidence generation based on RCTs and RWE studies. A strategic planning exercise to plot out multiple RWE studies to complement an established RCT plan can also be an effective approach.

When developing plans for RWE studies, it is also important to consider the available RWD sources early, in parallel with defining the details of studies. This is particularly important if looking to leverage the growing number of 'novel' RWD sources, which offer a range of new possibilities in terms of clinically rich data in certain focus areas of interest e.g. cancer and rare diseases, as well as novel types of data including lab values, imaging, genomic, other 'omic' data, and unstructured clinical notes. This will ensure that the designed RWE studies are feasible, and that the evidence generated is as rich as possible. The BC Platforms' Global Data Partner Network provides the ability to source appropriate data to meet the exact requirements of each study, from multiple sources.

2. DEVELOP A ROBUST PRESPECIFIED PROTOCOL AND STATISTICAL ANALYSIS PLAN, AND SHARE PROACTIVELY

A common mistake when seeking to leverage RWE to support or demonstrate a product's safety and efficacy is failing to share a prespecified protocol and statistical analysis plan or SAP with the specified regulatory agency. Taking a proactive approach and aligning with the FDA and EMA's RWE framework recommendations can help to guard against this risk. This includes ensuring that multiple analyses in electronic data sets are carried out quickly and inexpensively, making it possible to conduct numerous retrospective studies.[2]

Recent guidelines also recommend sponsors and requesting applicants provide draft versions of their proposed protocol and SAP for regulatory agency review and comment, prior to finalizing these documents and before conducting the study analyzes.[3]

The key objective is ensuring cross-sponsor stakeholder visibility to repeatable and audited analytics, and a clear iterative package that sponsors can bring forward for pre-submission alignment with regulatory bodies.

3. OPTIMISE VALUE FROM SELECTED RWD ASSETS

One of the most common causes for regulatory submission failure in RWE studies is 'data missingness.' This can be due to misalignment with 'real world' patient visit cadences and resulting data, when compared to the predetermined cadences of clinical trial visits and data collection. Aggregate level or claims data only do not suffice in telling the full patient journey and lack insight to physician notes and practice behaviors or reported outcomes

RWE based on clinically rich EHR data with additional enrichments like genomics, lab values, and imaging—can provide significant value in regulatory submissions, and help to achieve comparability with active trial cohorts. This is especially noteworthy within rare and ultra-rare disease populations. Having a global reach and catchment from which to source patient counts, confirm the regional incidence of disease, as well as to engage providers, sites and patients saves critical time, reduces patient burden, and can also enhance cohort sizes.

To achieve this, stakeholders need direct access to complete, row level longitudinal electronic health records (EHRs), lab values, imaging, genomic, other 'omic,' and sample data, without compromising on security or legal privacy requirements.

In cases where cohort sizes are inherently small, look to recent FDA guidance regarding data linkage and the combining of data as possible solutions. Data governance and quality control procedures not only ensure completeness, but data provenance as well. As these methods can also introduce new methodological challenges—notably around data heterogeneity—turning to analytics can help demonstrate data quality, statistical confidence, bias omission, and complete audits and audit trails.

A robust analytical architecture that will allow you to structure the incoming clinical multi-modal data, and stitch it together in a data fabric approach so that signals from various patient sources (omics, clinical research and outcomes data) can be combined is needed. Relevant patient signals and correlations will be picked up that will meaningfully contribute to the evidence of the therapy or product.

4. ENSURE ALIGNED RWE ACROSS DIFFERENT REGIONS

The fourth most common failure in RWE study acceptance is the challenge of variability in physician practice, standards-of-care, and outcome measure use across geographies, which can result in unclear outcome measures. It is imperative for pharmaceutical companies to carefully consider the geographies of interest to the relevant regulator(s) and carefully select RWD sources from geographies in which care provision closely matches care provision in the geography of interest to the regulator(s).

By considering a 'provider questionnaire phase,' qualitative insights can help to confirm standard-of-care practices within diagnostic and treatment pathways specific to their populations. Such a phase can provide an important risk mitigation strategy when developing data sourcing plans for RWE projects.

When incorporating underrepresented global populations within drug development, it is also critical to meet diversity and inclusion guidance that can underpin new market entries. Pharma companies must address the data needs and methodological issues, while in parallel aligning solutions that meet global regulatory guidance enforcements.

CONCLUSION

The bottom line? It is possible to overcome major areas of failure when using RWE in regulatory submissions. But the linchpin to that success is utilizing a vast network of provider sites to assemble the data within a GDPR+ technology platform and the analytics to enable access to the high-quality genomics and real-world data networks. Using a network of readily available line level patient data in analysis ready format, predefined statistical tools, visualizations, and advanced analytics can unlock previously untapped RWD assets from across the globe to accelerate insight generation for R&D and commercialization efforts. And those tangible results are accelerating drug development, healthcare provision, and clinical decision-making, which, ultimately, will positively impact patients and their families around the world.

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