The Return on Investment of Real World Evidence

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Introduction

As the patient's voice becomes more central to healthcare, it's necessary to demonstrate the value of medicinal products. As drug development costs continue to rise, real world evidence (RWE) generated from observational studies plays an important role in determining value as well as in decision-making.

The Food and Drug Administration (FDA) defines RWE as the "clinical evidence regarding a medical product's use and potential benefits or risks that is derived from analysis of real-world data (RWD), which are data relating to patients' health status and health care delivery, routinely collected from a variety of sources."[1] Examples of RWD include data from medical records, disease registries, mobile technologies (e.g., wearables), and social media platforms. In the rapidly growing RWD landscape, pharmaceutical companies increasingly invest in RWE, recognizing its conceptual value across the product lifecycle. There is, however, little consensus on the real value of investing in RWE.

RWE can fulfill critical needs throughout the medicine development and commercialization lifecycle. It results in a better understanding of the natural history and burden of disease, populations of interest, treatment pathways, and healthcare resource utilization, as well as patient experience with their condition and current treatments. Genetic and clinical RWD can support the genetic validation and phenotyping strategy in early discovery and facilitate clinical trial design and operations during the development phases at product launch and post-launch phases. RWE serves as inputs for clinical and cost-effectiveness models used by Health Technology Assessment (HTA) bodies and payers, which helps understand medication effectiveness, safety or adherence in clinical practice. It can answer interesting questions related to prediction of treatment outcomes, or the progression of a disease, or compare the effectiveness of treatments where head-to-head clinical trials are inappropriate – on occasion, using RWD derived "external controls", among other study designs.

The value of RWE is that it enables pharmaceutical companies to answer more strategic questions than ever before and continues to expand its reach. A variety of factors have contributed to this, such as the Big Data explosion, developments in digital and advanced analytics, and growing regulator, payer and physician acceptance. The consolidation of the value-based care model, where interventions are measured for their ability to improve patient outcomes against the cost of achieving these improvements, also plays a role.

These developments underscore the integral value of RWE and expanding opportunities for its use. Accordingly, biopharmaceutical companies are accelerating RWE adoption, investment and application.[1] However, some challenges remain; despite the important role that RWE plays across the pharmaceutical value chain, there are challenges that slow the progress of its capabilities, including a lack of internal understanding on how to use RWE.[2]

The increasing investment and use of RWE by pharmaceutical companies compounds the need to justify the return on the investment that it can bring. Some authors have already attempted to provide some estimation of the savings that RWE can bring to companies3, but a robust and consistent approach to measure the return on investment on RWE is not yet available. We provide a framework with metrics, detailed below, that can be used to describe and quantify the benefits of RWE to the life sciences industry, but first, let's review examples of companies capturing the value of RWE.

The value of Real World Evidence

As pharmaceutical companies continue to spend on RWE capabilities, it is important for organizations to establish qualitative and quantitative measures to assess the return on these investments. It is important to look beyond cost savings to assess value generation from RWE, directly linking it to favorable impacts on top-line sales or business objectives, such as a positive regulatory decision, speed to market, sales uptake in the market or interest through promotional claims, or influencing market access decisions. There are numerous analyses that demonstrate RWE can deliver significant value to the life sciences industry, impacting revenue and decision making.

Examples of companies capturing the value of RWE

1 – Clinical development: Real world data providing a synthetic control arm for Bavencio was critical for early regulatory approval

- **Goal:** The goal was to enter Bavencio to market quickly to address high unmet need for orphan- disease Merkel Cell Carcinoma (mMMC) with only single arm phase 2 trial data
- **Impact of RWE:** Through RWE use, they characterized the high unmet need and natural history of mMCC and provided a benchmark for comparison of the single arm trial results, showing ORR benefit was significantly higher with Bavencio than seen in the EMR database and patient registries with SOC

Key takeaway
- Bavencio reached patients in the US in 2017, 1.8 years earlier than other drugs in expedited pathways, providing therapy where none was available for mMCC (global sales of $113m in first 1.8 years)

2 – On Market/Commercial: Real world data supported differentiation of Entyvio vs other a-TNF, driving continued uptake in a crowded marketplace

- **Goal:** The goal was the differentiation of Entyvio vs many anti-TNF competitors to drive and sustain uptake in Crohn's disease (CD) and ulcerative colitis (UC)
- **Impact of RWE:** Results from a real world retrospective chart review announced in 2018, showed that incidence rates of both the first occurrence of a serious adverse event and serious infections, were much lower for those treated with Entyvio
- The EVOLVE (Entyvio Outcomes in Real-World Bio-Naive Ulcerative Colitis and Crohn's Disease Patients) RWE study showed lower incidence rate of first serious adverse events, a lower frequency of serious infections (SIs), and a lower percentage of gastrointestinal infections in biologic-naïve patients treated with Entyvio compared to other TNFα- antagonist therapy
- The US AGA guidelines now recommend Entyvio (or infliximab) over Humira in biologic-naïve patients. The UK BSG similarly re-commends Entyvio due to its long-term safety data. Entyvio sales continue to grow, reaching $3.3Bn global annual sales in 2019

Key takeaway
- RWE can complement a strong clinical program to drive sustained uptake in a highly competitive marketplace
- Long term commitment to data generation and publishing outcomes can support physician and patient confidence in product selection

3 – Regulatory: Real world data provided a historic control arm that drove accelerated and conditional approval in US and EU for Blincyto

- **Goal:** The goal was to demonstrate safety in a population for which a placebo group was unethical and bring Blincyto to market with only single arm, open-label phase 2 study data to address the high unmet need for patients with BCP
- **Impact of RWE:** Retrospective analysis of controls were used to show effectiveness and safety of SOC, providing a benchmark for Blincyto's phase 2 results
- Blincyto achieved FDA accelerated approval (2014), and conditional approval EMA (2015) as phase 3 trial was being conducted. It then achieved full approval based on phase 3 data (2017 FDA, 2018 EMA)
- Amgen's global sales of Blincyto totalled $360M from 2014-2017, and sales have now grown to almost $300M in 2019 alone. Amgen continues to generate long term outcome data, presenting 5-year survival data at EHA 2019

Key takeaway
- RWE can drive accelerated regulatory approval in orphan populations where a control arm may not be ethical or feasible
- Long term data generation supports continued uptake and product value
- For full approval and positive HTA recommendations, a comprehensive RCT program with a comparator arm is still beneficial

4 – Market access: Developing a RWE comparator to enable access to dabrafenib/trametinib for lung cancer patients in Canada

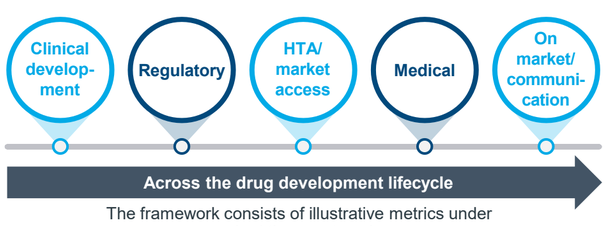
- **Opportunity:** BRAF V600 mutations occur in an estimated 2% of patients with NSCLC (~160 patients per year in Canada)
  - Dabrafenib/trametinib in BRAF V600 NSCLC was approved in 2017 based on a Phase 2 single arm trial
- **Challenge: Previous negative HTA opinion in 2L due to lack of comparator**
  - Clinicians and patient organizations advocated access for patients in Canada (high need for a targeted therapy option)
- **Impact of RWE:** Innovative HTA strategy RWD external control arm (ECA) enabled comparative effectiveness analysis with Phase 2 single-arm trial
- **Value story co-creation through robust advocacy plan:** Strong advocates rallying medical community. Continuous collaboration with patient organizations

Key takeaway: Positive HTA Recommendation in 2L NSCLC
- CADTH gave positive opinion based on ECA for Novartis submission
- Allowed for public pricing negotiation entry to enable access for lung cancer patients in Canada – opportunity to replicate ECA approach in other countries

A framework for measuring Return On Investment (ROI)

The RWE Leadership Forum developed a framework that outlines potential ROI for RWE. Mapped to the stage of the development lifecycle [Figure1], this framework helps assess the value and impact of RWE, support internal pharmaceutical company leadership in making informed investment prioritisation decisions, and drive the routine adoption of RWE. Designed to aid pharmaceutical leaders in quantifying the benefits and risks of conducting RWE studies, as well as the risks and down-sides of not conducting RWE studies, it creates a common language for discussing the value of RWE. Overall, success across this framework of metrics will ultimately drive benefits for patients through access to the right medicines at the right times

Figure 1. Outline of framework



The framework consists of illustrative metrics under each of these categories

The framework is constructed of specific metrics against the different components [Table 1], and indicates whether each metric has an impact on revenue, or an impact on decision-making

Table 1. Framework of key performance indicators

Category	Sample KPI	Revenue impact	Business decision-making impact
Clinical development	% of **trial protocols** informed by RWE[1]		X
	% of traditional RCTs transformed to pragmatic or single arm using **RWE external control**		X
	N° **sites** or **patient enrollment** identified via RWE		X
	N° of **new indication target** programs identified via RWE and initiated	X	X
	Clinical trial drop-out rate* where RWD is used in trial planning	x	x
	Clinical trial start up time* where RWD is used in trial planning	X	X
	% **clinical trial failure rates** where RWD is used in trial planning	X	X
	N° trials where RWD used to **increase representativeness and diversity**	X	X
Regulatory	N° of submissions (including label expansions) where RWE is considered "substantial" evidence for **positive regulatory opinion/topic closure**[1]	X	
	N° ODA/PIP acceptances (where RWE is a substantial component of submission)	X	
	N° **of post marketing regulatory commitments** substantially supported by RWE	X	
HTA/Market access	% **HTA submissions** including substantial contribution from RWE	X	
	% of submissions where RWE is considered substantial evidence for **positive HTA decision**	X	
	Time to access decision* (where RWE was a substantial part of the submission)	X	
	N° of instances in which RWE was a substantial part of **pricing negotiations**	X	X
	N° of products with **improved pricing/premium pricing decisions** (where RWE was a substantial part of the submission)	X	
	N° **managed entry agreements/value-based contracts** leveraging RWE	X	X
	N° **formulary inclusions** where RWE is considered substantial evidence	X	X

Category	Sample KPIs	Revenue impact	Business decision-making impact
Medical	N° of **prospective observational study** needs met through secondary use of existing RWD		X
	N° of **medical needs** met through secondary RWE approach[1]		X
	N° **clinical guidelines** (e.g., ESMO, NCCN) including product in relevant indications/LoT, where RWE is considered substantial evidence[1]	X	
	% TAs/products where RWD being used to inform and target **medical/sales force resource planning**	X	X
	% of **medical information requests** leveraging RWE	X	
On market/ Commercial	N° **innovative contracts** leveraging RWE		X
	N° of **promotional claims** leveraging RWE	X	
	N° of **health information exchange or field promotion** supported with RWE	X	
Across the drug development lifecycle	Time from study approval to insight/publications from RWE studies		X
	% reduction in **time to launch** through use of RWE	X	
	Reduction in **cost (and time)*** through use of RWE in place of e.g. RCT, PASS, LTFU[1]	X	
	N° **publications** of company-sponsored or led RWE studies (total and impact score)		
	N° **publications** referencing company-sponsored or led RWE studies		
	N° RWE studies bringing in the **patient perspective** (e.g., PROs)		
Additional supporting information to assess RoI*	**Probability of success** of RWE studies		
	Cost of RWE studies		

[1]Metrics currently being used by pharmaceutical companies

Some of these metrics are already used in the pharmaceutical industry[1], while the others will be useful in measuring value in the future – however, even in cases where metrics are captured, they are not always used to their full potential, leading to lost opportunities in demonstrating the return of investment of RWE. Indeed, the value of RWE is sometimes captured at a functional rather than global level, due to the siloed structures of some organizations, which could increase the risk of miscommunications and inefficiencies. Often, examples of RWE activities are communicated through "use cases" as a "proof of concept", rather than systematically implementing them into the organization, and rarely reach the point where RWE effectiveness is evaluated. To help rectify this, there is need for a comprehensive framework for applying an evidence generation strategy and method to quantify the return of investment of RWE that is implemented in a truly integrated way within a pharmaceutical organization.

How can the framework be implemented?

All companies differ in terms of their use, governance and impact of RWE. Precise definitions of these metrics may be challenging, and needs are likely to differ by type and size of company. The framework is therefore not prescriptive, but rather a set of options to support life science companies in identifying the most feasible and relevant key performance indicators (KPIs). The RWE Leadership Forum suggests that companies pilot the framework first, for selected studies and/or therapeutic areas, then update the framework for a broader roll-out. It is crucial in guiding pharmaceutical companies to quantify the value of RWE and measure the impact of investment on the overall portfolio performance. We suggest choosing a limited number of KPIs (5-8) that can be robustly measured and tracked, at least in the first instance, to understand the ROI of RWE, depending on the stage of drug development.

The implementation of this framework may not be heterogeneous across companies as there are notable differences in terms of how they use RWE, the governance that oversees it, and the data collected on its impact.

The estimation of the impact of a RWE study and the ROI is not straightforward because we cannot examine the exact same drug development lifecycle both with and without the RWE studies. Besides, when discussing the contribution of RWE to successful decision-making process other evidence packages may be considered, as it is difficult to isolate the individual impact of an RWE study on decision making.

The totality of evidence, including RWE, should be taken into account when making informed decisions.4 Given RWE is often part of a package of evidence, its value may be overlooked or discounted: This framework is meant to push the needle in conveying its value and significance in those packages and beyond in business decision making.

Additionally, companies can tailor the framework with new metrics to measure impacts across the organization. Initially, some effort will be required to collect KPIs for historic RWE studies in order to provide a benchmark. The framework will most likely evolve over time, as certain metrics translate into ROI more than others.

The framework can be adapted and used as needed by life sciences companies and serves as a starting point for companies to develop their own KPIs to help them understand the impact of RWE investment on overall portfolio performance.

Conclusion

There is substantial external pressure for the pharmaceutical industry to continue to innovate without increasing drug prices. RWE can help companies improve efficiencies and productivity to remain ahead of the curve in an increasingly demanding healthcare system. Pharmaceutical leaders can implement the framework to understand and demonstrate the value of up-front investments in RWE, generate evidence that meets stakeholder needs, realize efficiency savings, and evaluate the rate of return on RWE. The framework can then be customized with KPIs that measure their organization's specific needs.

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*% reduction versus internal company benchmarks