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Using Real-world Evidence to Advance Market Access for New Therapeutics

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This white paper includes key takeaways from the second session at Certara's first Strategic Evidence and Value Communications Symposium.

Building a successful drug development program and securing regulatory approval do not guarantee that a sponsor will achieve its desired price and market access for its new product. To achieve those goals, the sponsor must quantify the drug's value and develop the right strategies and insights to convey that value effectively to external stakeholders.

Sponsors need to demonstrate product value not just in a past clinical trial, which is an artificial construct, but objectively with high-quality, real-world evidence. Furthermore, that real-world evidence needs to be gathered with forethought about what core messages it will support. Payers need to know how a new product or technology will help them solve a public health management problem in their country, organization, or health insurance plan.

Getting an Early Start

This section summarizes a session presented by Oliver Leatham, "Advancing Market Access with RWE and Early Payer Engagement."

Engaging early in development allows sponsors to understand payers' and health authorities' perceptions better and enables them to address some of the uncertainties concerning their new product. It also lets sponsors explain how the new product will affect the current treatment paradigm and what value it will bring in terms of population health.

Some of payers' uncertainties regarding rare diseases and advanced therapies relate to the lack of comparative effectiveness data and the reliance on surrogate endpoints. These concerns can be overcome by understanding the predicted value of the product in the market post launch and being able to extrapolate early clinical data into meaningful, real-world information. It also helps to be able to predict the product's impact in terms of budgets and cost effectiveness.

Once it is clear how the predicted or assumed value will resonate with payers, the sponsor can determine what commitments it needs to make to back up those claims in the market. In other words, what real-world evidence needs to be collected?

Some key payer questions include: How should we pay for a treatment with great promise, such as chimeric antigen receptor (CAR) T-cell therapy, when there is no long-term benefit demonstrated at launch, but when all the costs are incurred up-front? How do we deal with high-cost curative therapies that may have a big budget impact in year one, but then less budget impact in subsequent years– particularly when health systems have annual budgets?

Figure 1.

Market Access Issues with Surrogate Data

Drug	Disease	Issue	Consequences & mitigation strategies
Glybera	Lipoprotein Lipase Deficiency (ultra orphan indication)	1st EC approved gene therapy Small patient population, no comparator, surrogate endpoint	Delayed launch (EMA approved in 2012) to collect 6-yr follow up data >€1 million per patient price tag. DE launched in Q4 2014, UK launch in July 2016. In May '16 only 1 reported sale in Europe
ataluren	nmDMD (ultra-orphan indication)	Conditional EMA approval on Phase IIb data – only subgroup data positive (6 min walk test)	Rejected by SMC but has been approved by NICE under a Managed Access Agreement, whereby the drug is made temporarily available at a discount until more mature data is available
OPDIVO (nivolumab)	2L+ NSCLC	Trial terminated early Lack LT follow-up Uncertainty over DOT	Despite transformational LT survival benefit, claims have struggled to gain positive appraisals in some obligate cost/QALY markets (incl NICE & PBAC) in NSCLC. Economic stopping rule used in NICE ACD.
Repatha (evolocumab)	Hypercholesterolemia	Regulatory approval on clinical trials using surrogate endpoint (LDL-c)	Data sufficient for regulatory approval but not for reimbursement (not recommended by SMC and TLV, no added benefit-IQWiG, ASMR IV -HAS). Ongoing trials to measure CV outcomes
Otezla (apremilast)	Chronic Psoriasis and PA	Seen as innovative by NICE but not as value for money. Not seen as cost-effective by IQWiG	Strong efficacy and safety data but limited cost-effectiveness data. Approved in August 2016 by NICE based on a confidential discount and use in only severe patients.
Abraxane nanoparticle albumin bound paclitaxel	Pancreatic cancer	Significant increase in OS but only 1.8 months and no QOL data collected	HAS – deemed ASMR IV versus generic comparator, led to exclusion from the liste en sus and being only reimbursed under a DRG – i.e. low prices and limited access

Much can be learned from past experiences (see Figure 1). For example, Glybera was approved by the European Medicines Agency (EMA) in 2012 to treat an ultra-orphan disease, lipoprotein lipase deficiency. But four years later, only one patient had received the product and been reimbursed. Eventually, the product was removed from the market.

The feedback was that Glybera's value was not communicated, understood, or accepted by the payer community. And with so few patients taking the product, both in clinical trials and the real world, no clear benefits were shown from the clinical data.

Repatha is another powerful example; its assumed value was based on a surrogate endpoint – the reduction in cholesterol LDL-c levels. But it was not market tested. While the Health Technology Agency agreed to that approach, payers pushed back. The payers wanted to know how the lower LDL-c levels would translate into reduced cardiovascular events, myocardial infarctions, and strokes.

The sponsor responded with a commitment to the payers to collect retrospective data that would demonstrate improved cardiovascular outcomes and reduced cost of care for those patients. This approach eventually drove successful market access, but the sponsor lost significant time in market.

Successful examples of communications engagement can be seen with the first CAR T-cell therapy launches in the UK – Kymriah from Novartis and Yescarta from Gilead. Both companies engaged early with payers and understood that there was considerable

uncertainty about the proposed high price of the products and the long-term data. They also engaged with multiple agencies – the National Institute for Health and Care Excellence (NICE), National Health Service (NHS) England, and Cancer Drug Fund. Through those discussions and negotiations, they agreed upon a price premium based on a commitment to real-world data collection, a review of those data, and a review of the reimbursement in 2023.

Xolair provides another example of effective engagement with national bodies in France. To address uncertainties at the Xolair launch, Novartis developed a predictive cost-effectiveness model which showed the drug was likely to produce a significant reduction in the number of hospitalizations for patients with acute asthma.

The resulting agreement involved a real-world evidence study jointly created by the sponsor and the health authorities. The study validated the predictions made about the product and led to considerable access and reimbursement.

These examples highlight how early value development, good communication, and a commitment to collecting data can help to demonstrate product value. This approach allows sponsors to align their commercial strategy with market demands, gain vital information regarding a product's real-world value and potential price, and often accelerate time to access and overall market uptake.

Furthermore, the Federal Joint Committee (G-BA) in Germany has required sponsors of rare disease drugs to have a real-world evidence protocol ready at launch. Then, the G-BA reassesses the product over a specified period to determine its effectiveness.

For a sponsor, employing real-world data can make the difference between having to launch a new product at a huge discount and negotiating a deal that allows it to gain and maintain a price premium. Real-world evidence that is economically quantifiable, such as reduced hospitalizations with Xolair, is the most potent. It is great to have quality of life data as well, but those tend to be softer outcomes, which are harder to measure financially.

Creating a Real-world Evidence Plan

This section summarizes a session presented by Kishan Vyas, "Challenges in Real-World Evidence (RWE) and Communication.

Regulators use real-world evidence to track safety and efficacy post-approval via post-authorization studies.

National public health decision making bodies, such as NICE or G-BA, use real-world evidence to provide contextual information when making reimbursement decisions for new medicines or new indications that are coming onto the market, and to monitor the ongoing value of a medicine in the market. Even if a drug obtains coverage and reimbursement, it does not mean that it will maintain it. In many countries, both formal and informal processes are applied to re-assess coverage using real-world evidence.

Physicians and prescribers use real-world evidence to inform clinical management. When new medicines are launched, many clinicians and payers are not familiar with the products. Real-world management experience is needed to help inform them.

Patients also play a much bigger role in treatment discussions with their healthcare providers these days and potentially use real-world evidence to help inform their treatment choices. During the COVID-19 pandemic, for example, strong opinions were expressed among patient communities, especially regarding vaccines. Therefore, it is important for sponsors to begin

engaging with patients and patient groups at the start of a clinical program. Sponsors need to understand the patient perspective early so they can use that insight to shape their evidence strategy.

Sponsors also use real-world evidence for a variety of needs, including to support regulatory filings, reimbursement applications, post-marketing monitoring requirements, and just to simply inform medical practice throughout a products' lifecycle.

One of the first steps that needs to be taken when developing a real-world evidence plan is to identify what data sources are available both internationally and at the affiliate level and the potential differences between them (see Figure 2). This process highlights existing data that can be mined and prospective or retrospective data that needs to be collected. The sponsor's team capacity to implement new solutions must also be determined.

Figure 2.

The Challenges of Developing a Global Vs. Affiliate RWE Strategy

Global Level

- RWE strategies and operations at companies (especially smaller companies) driven at global level
- Can be very USA centric
- Have larger resources in general
- Some affiliates may not get value from global driven studies due to specific in-country healthcare environments

Affiliate Level

- Affiliates generally have more finite budgets for evidence
- Have to be more innovative
- Will have more country-level needs due to healthcare environments differing country-country
- May have evidence gaps not reflected in the global plans

Many sponsors' real-world evidence strategies are led at the global rather than the affiliate level and those strategies are often driven by the United States because that is the biggest market for many organizations.

That approach poses challenges at an affiliate level because the healthcare system in every country is different, and therefore the evidence generation strategies employed also need to be different.

Global teams have greater resources and can conduct larger studies. Affiliate teams, with smaller budgets, need to be more innovative in how they generate evidence.

Furthermore, globally driven strategies sometimes don't yield the value needed for the local, affiliate healthcare environment. Therefore, affiliates must consider their own evidence generation, conduct their own mapping, and identify evidence gaps.

The key stakeholders may also differ between countries. Stakeholders include national organizations, local commissioning groups, government groups and the media in addition to regulatory agencies, healthcare professionals, patients, and patient groups. This adds another level of complexity to real-world evidence generation and communication plans because these stakeholder groups need to be involved early in the lifecycle of the medicine.

To help manage this complex challenge in Europe, for example, a common protocol is developed that meets the needs that are common to all the countries. The plan's execution is supported by all the local affiliates, and they also localize it to focus on outcomes that are important for their healthcare environment.

When people think about real-world evidence, they tend to focus on observational data from standard Phase 4 studies. However, validation can also be provided for payer groups using other types of studies and technologies.

While the evidence that needs to be collected is being determined, the best channel for disseminating that information should also be identified. Is it evidence that the sponsor's sales team will communicate to patients or data that its sales representatives will discuss with clinicians? The planning needs to be done early so that all the messaging is ready to communicate at the appropriate time.

Randomized Control Trials Vs Real-world Evidence

This section summarizes a session presented by Sumeet Bakshi, "Advancing Market Access with Real World Evidence."

While the goals of a randomized control trial (RCT; see Figure 3) are to establish safety and efficacy, real-world evidence is more versatile and can be used to establish clinical, economic or outcomes effectiveness, and even safety. Real-world evidence also represents real-life scenarios as opposed to experimental situations created in RCTs. There is a lot of variability in real-world evidence, whereas homogeneity is enforced in an RCT in terms of design, population selection, treatment, patient follow up, measurements, and derived definitions.

Figure 3.

Real-World Evidence (RWE) vs. Randomized Clinical Trials (RCT)

	RCT	RWE
Purpose	Establish efficacy and safety	Establish effectiveness (clinical, economic, humantistic etc.)
Setting	Experimental	Real Life Practice
Design	Experimental	Observational
Variability	Forced homogeneity in population selection, treatment, follow-up, measurements, definitions	Typically more variable in all aspects. Could have extreme variations in some situations
Monitoring	Intense	Not applicable
Data quality	High	Variable
External validty	Low	High

The real world varies in how treatments are administered, and how patients take them, and even in how diseases are defined. There are also variations in coding between patients and practices.

The monitoring required on an RCT is intense. Whereas with real-world evidence, there is no monitoring; it is free-flowing data coming in from the real world.

Data quality is high with RCTs, so their acceptance is extremely high, but the data cannot be generalized. In contrast, data quality can be variable with real-world evidence, but the acceptance and validity can be high.

Communication of Scientific Research is Evolving with RWE

Results from RCTs were traditionally communicated via scientific publications, slide presentations and evidence dossiers, or incorporated into budget impact or cost-effectiveness models.

RCT messaging was predominantly centralized, driven by global teams, and implemented by affiliates in their own way. But the core messaging was very centralized.

In contrast, real-world evidence enables distributed messaging; it requires communicating relevant messages to a diverse and complex stakeholder group (see Figure 4). Real-world evidence also offers the opportunity to present local, pertinent evidence pertaining to smaller populations – population substrata – to stakeholders. This can be accomplished using interactive tools, dashboards, visualization software, and digital communication media.

Figure 4.

RCTs and RWE have different strengths regarding communication with stakeholders

Key attributes of a communication strategy for all stakeholder groups	Traditional media for communication of RCTs	RWE enabled innovative media
Understandable		
Actionable		
Accessible		
Credible		
Relevant		
Timely		

RCTs are well understood by the scientific community, but not by laypeople. Whereas real-world evidence is more accessible and better understood by the public. RCTs can be actionable, and they are more credible. Real-world evidence can be interpreted in different ways, so it is even more important how that messaging is distributed and controlled so that it remains consistent.

RCTs are relevant only to the population that was studied in the trial, whereas real-world evidence can be relevant to individual stakeholders.

The biggest difference between real-world evidence and RCTs is the time limits. Clinical trials take their own time, even under the expedited conditions seen for the COVID-19 vaccines trials during the pandemic. Real-world evidence can be made available in a timelier manner to audiences, especially through live dashboards. Digital tools permit more planning and allow a common thread to be included in all communications to diverse stakeholders.

Conclusion

The best advice for using real-world evidence to communicate a new drug's value is to begin planning as early as possible. Also, start evidence collection and communication planning at the same time. Then, explore all the relevant communications channels and consider how the messaging is going to be interpreted by each stakeholder at the global and local level. Real-world evidence is a powerful tool when handled appropriately.

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