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Tackling RWE Challenges To Demonstrate Healthcare Value

by

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Much of the debate across the healthcare continuum continues to focus on value and value frameworks in the US and health technology assessments in a regulatory context and reimbursement content, ex-US. Different stakeholders – whether producers, payers or patients – may pick and choose which real world data points they wish to emphasise and then convert into RWE. Fortunately, there is a growing body of evidence highlighting how companies are overcoming these challenges and embracing RWE.

Real world data (RWD), the underlying data supporting the generation of RWE, encompasses all information generated in routine medical practice such as electronic health and medical records (EHR), claims data, pharmacy data, and clinical outcomes assessments. It also includes epidemiological data, registry data, health survey data, plus a host of new forms of information such as social media data, wearables-derived data, sensor and behavioural data.

Large scale computational power to apply against RWD is becoming increasingly affordable and accessible to all stakeholders. As such, this creates greater opportunities for real world insights into patient behaviours, treatment costs and drug performance.

The US Food and Drug Administration defines RWE as evidence generated from real world data in a highly pragmatic way. One of the main arguments in favour of using real world data is that clinical trials are often too narrow, excluding too many people and are not pragmatic enough. Consequently, trials have been conducted that do not represent how the drug might perform in a real world setting.

The Salford Lung Study is a much cited example of a real world effectiveness trial in that it demonstrated a higher magnitude of effect in the real world than had been seen in a randomized controlled trial. Conducted in 75 general practices in and around Manchester in the UK, and sponsored by UK pharma GSK, the study compared the effectiveness of fluticasone fluorate/vilanterol to maintenance therapy in treating patients with chronic obstructive pulmonary disease (COPD). Published in the New England Journal of Medicine in September 2016, the study found that the rate of moderate or severe COPD exacerbations was significantly lower by 8.4% with the therapy than with standard care.

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Other trials that have an RWE component are already in the works. Sanofi, the French pharma major, is sponsoring ACHIEVE CONTROL, an observational study enrolling 3,324 patients and due for completion in July 2018. The study is designed to assess the clinical and health outcomes of Toujeo (insulin glargine) compared to commercially available basal insulins for initiation of therapy in insulin-naïve patients with uncontrolled Type 2 diabetes. The key metric will be the proportion of patients with individualized HbA1x target attainment at six months without documented hypoglycemia.

Novartis, the Swiss pharma, is sponsoring PANGEA 2.0 an observational study involving 1,500 patients that is due to complete in March 2020. The study has been designed to examine the long term benefit of switching multiple sclerosis patients with disease activity, following treatment with currently available drugs, to Gilenya (fingolimod). Therapeutic efficacy of the switch will be evaluated by modified Rio score, NEDA-4 and 2D focussed disability score. PANGEA 2.0 will also assess new forms of data acquisition and the predictive power of proposed treatment using the MSDS 3D patient management system.

RWE is being used in different forms by regulatory authorities. Pharmacovigilance is a

mandatory requirement from several regulatory authorities and that, in most cases, is based on real world data. Regulators are increasingly asking for commitments from drug developers for post-marketing safety studies as a condition to product registration and approval. Indeed, the FDA has made progress on using RWE within rare disease drug development and post-market safety surveillance. It has been used, for example, to support the approval of New Drug Application (NDA) submissions for rare diseases or in small population settings.

A study published in the Journal of the American Medical Association (JAMA) 9 May 2017, highlights the importance of post-approval surveillance of safety issues. The study examined 222 novel drugs and biologics approved by the FDA between 2001 and 2010 and noted that there were 123 post-marketing safety events – 59 safety communications, 61 boxed warnings and three outright product withdrawals – impacting 71 new therapeutics.

Regulators and policymakers are starting to look at how to incorporate RWE in product assessments. The US 21st Century Cures Act requires the FDA to develop guidance for using RWE to support approvals of new indications for existing drugs and post-approval study requirements. In the US, the FDA published final guidance on the use of RWE for regulatory decision making for medical devices in August 2017 and has announced plans to publish draft guidance on the use of RWE for the assessment of safety and effectiveness in regulatory submissions before the end of 2021.

Similarly, the European Medicines Agency (EMA) adaptive pathways program, in principle, embraces greater use of RWE to support conditional approval and/or expansion of indications once a product is initially approved in a narrower population.

Indeed, in a bid to provide patients access to innovative but often expensive medicines – usually cancer drugs – a number of European countries have introduced managed entry agreements. These can take many different forms although finance-based schemes are more prevalent than performance-based ones. Finance-based MEAs range from simple discounts to more nuanced price and volume caps. Performance-related MEAs, most frequently used by Italy, are designed to determine refunds for non-responders and involve patient registries managed by the Italian Medicines Agency (AIFA) to allow sharing other clinical information and safety data between regulators, clinicians and pharmacists.

Real World Examples

Several drugs have been approved with real world data. Amgen used RWE to supplement a clinical trial of Blincyto (blinatumomab), its drug which received accelerated approval from the FDA in December 2014 for treatment of acute lymphoblastic leukemia. Amgen submitted a single study as well as a historical comparator arm of patients who received standard of care as the control arm. The company reported a significant treatment response in the Phase II single arm study and two years later, when publishing its Phase III randomized, open-label TOWER study,

obtained the same median overall survival of 7.7 months for Blincyto versus 4 months for standard of care.

Similarly, Alexion Pharmaceuticals Inc managed to secure an extension to the label from the European authorities when investigators used a disease registry to obtain a comparator group to measure the efficacy of Soliris (eculizumab) as a treatment of paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis. Initially, the drug's use had been restricted to patients with a certain disease severity.

Novo Nordisk is investing significant effort in generating RWE to support its diabetes franchise. RWE from a post-marketing study conducted by but requested by the French authorities for the GLP-1 agonist Victoza helped broaden the product's label to an additional patient subgroup in Quebec. Moreover, the Danish pharma believes two RWE-generating studies around the long acting insulin Tresiba, launched in Europe in 2013 and in 2016 in the US, both highly competitive and price-sensitive markets, will strengthen the company's positon in pricing negotiations, beef up its marketing communications and enhance its value dossier in markets where the product has yet to launch.

While much of the focus is on using RWE to get regulatory approval of drug applications, it can also be used for clinical practice guidelines to decide how to best manage patients, for payers deciding whether to pay for a drug, and for comparative effectiveness.

Highlighting The Value Proposition

Eli Lilly & Co used real world data to size the single-use vials for its recently launched IV cancer drug Lartruvo (olaratumab) in an effort to reduce potential waste and cost of treatment. An analysis of population-based weight and body surface data, from more than 240,000 oncology patients, informed the decision to develop a 190mg vial alongside the original 500mg Lartruvo vial. The company reckons the trade-off is a cost reduction of $1,132 per patient per administration.

Japan's Takeda says RWE has confirmed the benefits of its best-selling inflammatory bowel disease therapy Entyvio (vedolizumab) in US medical practice. RWE collected in the US conformed the efficacy of the drug, first launched in the US in 2014, as a treatment of ulcerative colitis (UC) and Crohn's disease. The company believes the Entyvio RWE will help the IBD community decide on the drug's role in their medical practices.

Indeed, the VICTORY (vedolizumab for health outcomes in inflammatory bowel diseases) consortium of ten IBD medical centers reported on a cohort of 180 patients with moderate to severe active UC, who were treated for 12 months in routine practice, and followed through electronic medical record searches, review of clinical records or by questions addressed to the centers. Some 77% of patients achieved mucosal healing, defined as having a Mayo endoscopic

subscore of zero or one, while 51% of patients had a clinical remission and 41% had a steroid-free remission.

Defending Optimal Pricing

While RWE does not guarantee access, it is clearly having an impact on the thinking of payers. Indeed, RWE originating from, for example, patient registries, EHRs, claims data or cohort studies, is likely to become an increasingly important means of supporting innovative pricing and outcomes-based contracting strategies, proving the value of medicines to payers, potentially improving the probability of winning reimbursement.

Following a health technology assessment (HTA), NICE, the National Institute for Health and Care Excellence, who is responsible for assessing that the National Health Service of England and Wales is getting value for its money, changed its mind and decided to recommend Johnson & Johnson's Zytiga (albiraterone acetate) for chemotherapy-naïve metastatic castration-resistant prostate cancer patients after the company presented RWE from US insurance claims data.

Many managed entry agreements or risk sharing deals in Europe rely on gathering real world data. France agreed to reimburse Celgene Corp.'s Pomylast (pomalidomide) for multiple myeloma under a risk-sharing scheme. The company will have to repay the cost of the drug if a patient does not respond to the treatment. Risk-sharing schemes are also in place elsewhere in Europe, while a recent evaluation of NICE submissions has revealed that RWE drives HTA approval in 86% of submissions.

Regulators are increasingly using RWE to monitor any post-approval safety concerns. This has been particularly useful when looking at novel anticoagulants especially when compared with industry mainstay warfarin. In recent years, more than 100 observational studies have been published on real world use of anticoagulants. In the US, these have typically used claims databases from Medicare and Medicaid, while the European studies have relied upon national databases. Importantly, it appears that the anticoagulants behave in the real world as they did in clinical trials.

One huge potential source of data is the FDA's Sentinel program which houses electronic health care data for more than 223 million individuals – about half the US population -- from health plans, health care systems and academic medical centers. Moreover, the number of individuals in the network will increase in the coming years with the addition of data from the Centers for Medicare and Medicaid Services. Indeed, the large and growing number of patients covered by the US FDA's Sentinel electronic data network offers drug sponsors looking to satisfy post-market safety requirements using real world data an extensive data set. Having participated in a pilot program, Pfizer also noted the potential to look beyond post-approval safety signals. The company noted that Sentinel could also be used to conduct drug utilization studies to look at off-label uses as well as questions around appropriate use.

Not surprisingly, Boehringer Ingelheim has used real world data to build its case for its direct thrombin inhibitor Pradaxa (dabigatran), the first of the new generation of anticoagulants. The company has enrolled 34,500 patients in the GLORIA-AF study and plans to include a total of 56,000 in the registry. So far, the company has been running observational studies but is considering ways of doing prospective pragmatic trials in the future. Possibilities, as the field evolves, include running real world trials to support supplemental indication filings with the FDA.

Pfizer, the world's largest pharma company, is leading the use RWE at almost every stage of a medication's life cycle. The company conducts a significant amount of non-interventional research. For retrospective studies it uses de-identified secondary data sources such as insurance claims and EHRs to evaluate epidemiology, treatment patterns, clinical outcomes, healthcare resource use and costs associated with a treatment of disease. Moreover, patient data generated by wearables, apps or even tapping into social media will become an important source for understanding patient needs and behaviours.

Typically, the company will provide RWE on epidemiology and unmet needs through analysis of secondary data sources and collecting information from patients, physicians and payers. Real world data is also often included in economic models, while supplemental information, such as healthcare resource use, productivity loss and out of pocket expenses, is collected during the running of clinical trials. Following launch, companies may conduct comparative effectiveness research to either identify and understand sub-populations or provide value differentiating evidence.

While there is an expectation that all pharma companies will need to have RWE strategies in place, one of the biggest roadblocks in using RWE for regulatory purposes is the inadequate data in electronic healthcare records (EHR). This is because the traditional outcome measures that are used in conventional drug development are not generally found in EHRs. The challenge is that much of the needed clinical information is stuck in the doctor's notes as unstructured data. Advances in machine learning and natural language processing are expected to provide some resolution to this challenge and enable practitioners to mine the gold buried deep within unstructured clinical notes within EHR.

Moreover, as most sources of real world data are not actually collected for research purposes, data quality is an issue. EHRs, for example, are primarily intended for patient management, rather than for research, and there is a clamour for more alignment across all stakeholders to develop consistent data structure and gathering methods. Indeed, transitioning from an ad hoc to an industrial approach to curating RWE will require collaboration and investment from all stakeholders. Regulators, in collaboration with the pharma industry and payers, still need to formulate robust standards for RWD collection from a variety of sources.

Motivating this are are manufacturers, payers and third parties, who are looking beyond their own walls to establish the true value of medicines. Most value-based contracts to date have been bilateral and payer population- specific, where the manufacturer and the payer share data. An alternative option would be to include broader sets of relevant RWD – including data generated by third parties – into the parties' value-contract adjudication calculations. This would have stakeholders seeking out additional appropriate sources of data to analyse, not necessarily just a specific payer's population, but an even larger representative real world population set in order to reduce administration costs and potential conflicts.

While such data sharing for value-based contract administration purposes is not commonplace, industry has long been quite content to use third-party generated data to administer prescription market share-based contract. Indeed, reliable and independent third party data can be important in subsequent value-based contract negotiations.

RWE clearly has huge potential to inform healthcare stakeholders – whether manufacturers, regulators, clinicians, patients or payers. While there are still multiple challenges with RWE becoming a consistent mainstay of the healthcare regulatory oversight and commercial performance insight, it is clear that there is an appetite among all stakeholders to resolve them. Big data capabilities and linkage of data sources will drive an increased development and application of real world evidence.

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Mike has over 20 years of executive experience with global biopharmaceutical firms and digital health start-up ventures, leading commercial strategy, payer and specialty pharmacy account management, market access contracting and operations, sales, sales training and leadership development functions. At EMD Serono, he instituted the outcomes-based contracting effort that led to the first outcomes-based agreement on a specialty medication with a health plan, followed by the first outcomes-based agreementwith a pharmacy benefit manager in the United States.

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Jim Carroll leads ICON's Real World Evidence Strategy & Analytics group, which develops real world data (RWD) and technology based solutions to support sponsors who are seeking to expand labelling and market access, while staying ahead of the growing demand for evidentiary requirements. Jim has over 20 years' CRO and pharmaceutical experience. He joined ICON from inVentiv Health, where he led the formation of a new business unit focused on providing novel RWD-driven services.