Real-World Evidence: A Better Life Journey for Pharmas, Payers and Patients

Using RWE, the entire healthcare ecosystem can use actual health outcomes to better assess the value of drug treatments and related services.

Executive Summary

Randomized control trials (RCTs), the established way for measuring the safety and efficacy of drugs, are increasingly being challenged by payers and healthcare providers. These players in the wellness ecosystem are asking for real-life data to validate whether new drugs provide similar safety and efficacy as indicated by RCT results.

With RCTs, the results are obtained in a highly controlled environment, over a small set of patient population, over a short period of time, across a handful of highly dispersed clinical trial centers. Questions are being asked by the Federal Drug Administration (FDA) regarding the sole dependence on RCTs and the lack of real-life supporting evidence by pharmaceuticals companies on the efficacy and effectiveness of new drug treatments. This is driving an increase in drug recalls, including those of blockbuster drugs such as Xigris by Eli Lilly, Avandia in 2010 (in Europe, only) by GSK, etc.

This white paper details our point of view on ways the pharma industry can apply real-life data to more effectively gauge drug treatment effectiveness and efficacy, enabling the entire ecosystem of providers, payers and patients to deliver “wellness” to all constituents.

Defining RCTs

RCTs as a mechanism for evaluating the efficacy of the drug cannot be replaced (as controlled environments are needed to separate the impact of medical interventions). Two measures are important to define:

- **Efficacy** is the extent to which an intervention does more good than harm under ideal circumstances.
- **Effectiveness** is the extent to which an intervention does more good than harm when provided under the usual circumstances of healthcare practice.

However, to evaluate the cost-efficiency of a drug in a real-world environment and gauge its impact on improving the quality of healthcare, RCTs need to be supplemented or followed up with the comparatively new standard, called real-world evidence (RWE).

When it comes to pharmaceuticals, all wellness stakeholders today require “evidence.” Patients are looking for a better end result with their treatment. Providers are looking for data-oriented proof that the prescribed drug helps to optimize patient treatment, and brings added cost-efficiency and better profit margins. Payers (both
government and private) are asking providers and manufacturers to prove and promote the benefits that they will reimburse for in their healthcare systems. Regulators, from the overall public health and well-being perspective, are also looking for evidence in a real-world environment. With all these pressures, pharma manufacturers are forced to think “evidence” — and the time has come to think beyond the controlled environment of clinical trials.

**RWE vs. RCT**

But what exactly is real-world evidence? It uses observational data to generate insight, foresight and predictive findings on diseases, products and patient populations. Figure 1 depicts the differences between RCT and RWE.

**RWE Data**

So what is real-world data? It is “observational data” — data that involves the information related to a patient’s treatment. Typically, this consists of four revealing data types that have overlapping and distinct characteristics — patient claims data (available typically with payer), patient registries (available with provider and payer), electronic health records (EHR)/electronic medical records (EMR) and Web/social data. Figure 2 offers a deeper explanation.

**Application of RWE Data**

The straightforward and most imminent application of real-world data is defending or improving market access compared with the competition through “comparative effectiveness research.” However, it is not limited to this application. The following analytics applications typically depend on real-world data.

- **Comparative effectiveness research/optimal treatment algorithm:** Comparés alternative treatment regimens, drugs and dosage on multiple criteria — cure, adverse effects, cost, etc. — to arrive at the best treatment option for particular diseases for particular patient profiles defined by demography, family disease profile and comorbid conditions. While historical data mining is important here, proactive strategy on patient targeting and pharmacovigilance via predictive analytics is gaining popularity.

- **Patient adherence study:** A related area of importance is the patient adherence study. While for a manufacturer or provider non-adherence means a lower observed effectiveness compared with what is expected, for payer and regulator it means increased healthcare costs. Patient segmentation based on their chances of becoming non-adherent may help design a targeted educational program. If the non-adherence reason, as suggested by data analytics, is hidden in the drug or treatment methods itself (i.e., twice-a-day vs. once-a-day treatments, pills vs. injectibles, invasive vs. laparoscopic, etc.), it may also suggest product or treatment innovations that may be needed.

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**Figure 1**

<table>
<thead>
<tr>
<th>Randomized Control Trial</th>
<th>Real-World Evidence</th>
</tr>
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<tbody>
<tr>
<td>Patients are randomized to the treatments; physicians’ and patients’ choices are not considered for selection of the treatment.</td>
<td>Therapy or medications to patients are determined by doctors’ choices as per the standard practice.</td>
</tr>
<tr>
<td>Non-adherent patients are taken out of the analysis.</td>
<td>Non-adherent patients can switch the treatment and in such a case are likely to remain included.</td>
</tr>
<tr>
<td>Experiment is based on an artificially created homogeneous treatment group. The purpose here is to establish the efficacy of the medication/therapy.</td>
<td>Contains heterogeneous patient population reflecting realistic scenario. The study is likely to indicate the effectiveness of the drug/therapy under various conditions.</td>
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Outcome-based pricing/contract: Payers in both government and private sectors are challenged by increasing healthcare costs. To counter this challenge, they are overly cautious regarding how they spend constrained budgets and are seeking return on investment justification in advance of making any outlays. Many are establishing their own therapeutic guidelines over and above what is required by regulation. To land in the right plan and price category, pharma companies need to provide payers with supporting evidence based on real-life data to document drug treatment efficiency and cost-effectiveness.

Clinical research feasibility: Real-world data can evaluate the feasibility of the RCT protocol by judging whether there actually will be enough patients to be recruited to participate in a clinical trial or, from a commercial perspective, whether a study can really reflect the conditions of the target population if the pool is limited. RWE can also help to determine the potential investigator and the potential site, based on the patient composition.

RWE-Led Pharma/Payer Partnership
As the need for RWE is mutual, manufacturers and payers are already strengthening their bonds.

### The Four Categories of Real-World Data

<table>
<thead>
<tr>
<th>Patient Claims</th>
<th>Patient/Medical Registries</th>
<th>EHR/EMR</th>
<th>Social Data</th>
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</thead>
<tbody>
<tr>
<td>• Hospital claims: episode-level information.</td>
<td>• Patient registry refers to a collection of patient/diseases/therapy-related-information collected through the observational study method of patients, physicians and laboratory tests.</td>
<td>• The electronic medical record is a patient-level electronic record of health information collected from a single provider practice. An electronic health record is a similar concept, but it goes beyond a single provider practice and data are generally collected from multiple healthcare practices and hence would follow nationally recognized and standardized practice.</td>
<td>• This relates to patient interaction on diseases, treatment experiences and side effects. Social networking sites such as Facebook and Twitter have pages specific to diseases and medications. Sites such as Medhelp, PatientsLikeMe, CureTogether, Diabetic Connect, Disaboom also allow patients to form communities, groups and discuss experiences.</td>
</tr>
<tr>
<td>• Provider claims: procedure-level information.</td>
<td>• Registries are focused on target populations and are designed to fulfill specific purposes defined a priori. For example, they include: product registries (patients exposed to a particular drug or medical device), health services registries (patients with common procedure/clinical intervention/hospitalization) or disease registries (patients with similar diagnosis).</td>
<td>• EHRs are not focused on any particular product, healthcare services or disease-based target population.</td>
<td></td>
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<tr>
<td>• Prescription claims: prescription-level information.</td>
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</tbody>
</table>

### Data Elements

<table>
<thead>
<tr>
<th>Patient claims information.</th>
<th>Patient reported data: demographic information, patient reported outcomes (PROs).</th>
<th>Patient demographic information.</th>
<th>Unstructured texts, dialogues, sentiments as expressed by the patients or their kin (in cases where the patient is managed by his or her kin).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient demographic information.</td>
<td>Clinician reported data: diagnosis, treatment/drug prescribed, laboratory/clinical test suggested, follow-up treatment physician rating of effectiveness.</td>
<td>Patient and family disease history.</td>
<td></td>
</tr>
<tr>
<td>Consultation details.</td>
<td>Laboratory: diagnostic/clinical test results.</td>
<td>Patient physical report.</td>
<td></td>
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<tr>
<td>Hospitalization details along with cost of treatment.</td>
<td></td>
<td>Consultation details.</td>
<td></td>
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<tr>
<td>Diagnoses.</td>
<td></td>
<td>Hospitalization and discharge details.</td>
<td></td>
</tr>
<tr>
<td>Procedures/drug names with doses and days supplied.</td>
<td></td>
<td>Patient operative report.</td>
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Figure 2
For example, Healthcare, Wellpoint’s analytics division, has been collaborating with AstraZeneca since 2011. The objective of the alliance is for each partner to help the other to more effectively integrate data from disparate sources to understand evidence-based outcomes. In 2011, Humana entered into a five-year partnership with Pfizer to improve their healthcare delivery systems by improving the quality, outcomes and costs of treatment. Humana also entered, in 2013, into an agreement to sell its claims data to Eli Lilly, which will use it to estimate and predict patient outcomes, adherence and overall costs.

**New Techniques to Suit New Requirements**

While the origins of RWE are diverse, achieving RWE is not trivial. That’s because the big data sources are scattered and are composed of elements in various structures. For instance, they originate from social media platforms, claims data, medical records (electrical) and even published literature. Sometimes it is organized and structured and sometimes it includes minimal text and other elements (graphics, videos, etc.). This data can be everything and anything describing in bits and bytes the journey of the patient.

As a result, RWE is vast and varied in its type and also in its sources. The challenge: If it is so diverse, how can data be meaningfully analyzed for insights that can inform strategic decision-making? Two ways to glean insight from disparate data sources are the classical/traditional approach and the machine learning approach.

- **Classical/traditional:** It is taken as an axiomatic truth that data in a randomized control trial is generated by a given probability distribution curve. In essence, an RCT involves the testing of different causes and effects. The model used is influenced by parameter significance. If a parameter is not significant, then that particular factor is removed from the model. Bayes Rule is one such example as are duration models, principle components and many others.

- **Machine learning:** This is very different from the previous method. In this approach, algorithmic models are used. The data mechanism is treated as unknown. Predictive accuracy is the focus. And even if the model is not interpretable, predictive accuracy is prioritized. The basis here is the validation of such predictive accuracy. Partitioned data sets are used to accomplish this. Some of the examples are neural networks, regression trees, cluster analyses, support vector machines and random forests.

With the variety of data sources and structures, it is clear that ML techniques are better suited for RWE analysis. These techniques can play a very important role in RWE’s evolution and also in the production of robust RWE in what is known as data settings with highly complex mechanisms. ML techniques are better suited where insights are to be gained using unstructured or semi-structured data.

In the case of structured data, however, traditional approaches are still thought to be more effective, but only in statistical inferences and also while testing hypotheses. On the other hand, while it comes to finding critical growth drivers, predicting a trend and then determining non-linearities and interactions, ML techniques are again more effective.

Last, regarding mathematical/statistical techniques: At times, it may not be just one technique but rather a combination of statistical methodologies, often called “ensemble techniques,” that will provide better accuracy than individual techniques for a particular problem in hand.

**Looking Forward**

RWE provides the answer for understanding whether any treatment/service/care delivery method would perform in the real world as it would in controlled conditions. RWE, along with the data acquired from clinical trials, can provide a true picture of what is actually happening among patients. This data can be used to build a better and more complete understanding of the diseases and their patterns, thus providing better healthcare.

With more public databases available, there is a need to use the best analytical approach to address critical questions. The use of modern techniques has already begun. Once we have empirically-sound results, extra care must be given to project efficacy and effectiveness on the general population since there can be inherent limitations in those results.
Modern analytical techniques such as machine learning algorithms can bring radical positive changes in healthcare, but high-end analytics will not work unless pharma companies:

- **Make continuous investment** in the underlying tools and processes.
- **Reach a common objective** on which all stakeholders agree.
- **Embrace product-agnostic solutions** and overcome stakeholders’ reluctance to embrace advanced methodologies.

Once all these hurdles are crossed, there is little that can hold back the true power of real-world data.

References

- Understanding Health Outcomes and Pharmacoeconomics, George E Mackinnon III.

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