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Creating value from next-generation real-world evidence

Leading pharma companies are applying advanced analytics to real-world evidence generation to deliver impact at scale. How can leaders keep innovating, and what should others do to catch up?

by David Champagne, Alex Davidson, Lucy Pérez, and David Saunders

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As the healthcare industry focuses increasingly on outcomes, pharma companies are looking to sources beyond randomized clinical trials (RCTs) to measure and demonstrate the value they bring. Real-world evidence (RWE) has been in use for decades, but recent advances in digital and advanced analytics allow it to be employed in new ways. It can help us understand how patient characteristics and behaviors affect health outcomes—thereby helping to predict the progression of a disease, a patient's responses to a therapy, or the risk of adverse events, for instance—while also increasing the efficiency of R&D investments and accelerating time to market. For any company considering deploying advanced RWE analytics, success will depend on building the right framework and capabilities.

From table stakes to high stakes

Cost and competitive pressures, scientific advances, digital-savvy stakeholders, progressive regulatory shifts, and the increasing breadth and interoperability of data and technologies are among many trends driving participants in the healthcare ecosystem to intensify their focus on value and patient outcomes.

Payers are gradually shifting to outcomes-based contracts[1]; providers are angling to gain privileged status with them; and patients are taking more ownership of their own outcomes. In this changing environment, insights from real-world evidence are becoming more important in getting the right treatment to the right patient at the right time, measuring outcomes, and demonstrating the value of interventions. Given the significant disruption to RCTs and the need to rapidly understand burden by patient phenotype, and potential therapies for COVID-19, RWE is more in the spotlight than ever.

Pharma companies have been using real-world evidence for decades to inform their decision making, respond to requests from external stakeholders, and improve their therapies' market positioning. More recently, growing regulatory acceptance, rising demand from payers and physicians, and increasing familiarity with digital and analytics have enabled some companies to derive much broader benefits from RWE. Examples include Pfizer's use of electronic medical record (EMR) data in obtaining approval for Ibrance to treat male breast cancer[2]; Roche's use of a synthetic trial

Real-world evidence helps us understand how patient characteristics and behaviors affect health outcomes.

[1] See, for instance, "Amgen and Harvard Pilgrim agree to first cardiovascular outcomes-based refund contract for Repatha (evolocumab)," Amgen, May 2, 2017, amgen.com; "Harvard Pilgrim signs outcomes-based contract with AstraZeneca for Symbicort," Harvard Pilgrim, April 18, 2018, harvardpilgrim.org.

[2] "US FDA approves Ibrance (palbociclib) for the treatment of men with HR+, HER2- metastatic breast cancer," Pfizer, April 4, 2019, pfizer.com.

arm to secure reimbursement for its lung cancer drug Alecensa[3]; and AstraZeneca's use of real-world data to demonstrate the real-world effectiveness of its diabetes therapy Farxiga compared to competitors.[4]

In the past few years, the introduction of advanced RWE analytics has made real-world data an even more powerful resource for pharma companies. Unlike traditional RWE analytics—which uses descriptive analyses to characterize patients, and established matching techniques to compare groups of patients with similar characteristics—advanced RWE analytics uses predictive models, machine learning, probabilistic causal models, and unsupervised algorithms to extract deeper insights from rich data sets (see sidebar, "Comparing traditional and advanced RWE analytics"). It enables pharma companies to draw on thousands of patient characteristics to gain a better understanding of what drives outcomes, to uncover insights into drug performance and differentiation at sub-population level, to run accurate scenarios with predictive models, and to generate hypotheses at scale across multiple therapies, comparisons, and endpoints (Exhibit 1).

Exhibit 1

Advanced real-world-evidence analytics can play an important role across the pharma value chain.

R&D

Identify unmet need:
- Inform research decisions

Innovate in trial design:
- Use synthetic control arms

Improve trial design:
- Define inclusion/exclusion criteria and end-points
- Optimize site selection
- Accelerate recruitment

Accelerate time to market

Refine formularies:
- Determine optimal dosing based on patient response

Monitor real-world outcomes:
- Quantify unmet need
- Understand safety and efficacy profiles

Market access

Improve evidence of economic value:
- Demonstrate economic value of treatment to payer
- Compare trial data with real-world evidence (RWE) to strengthen dossier
- Enable outcomes-based pricing

Improve formulary position:
- Achieve better patient access
- Show efficacy and safety through head-to-head in silico trials

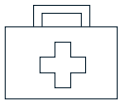
Achieve label expansion:
- Use RWE to eliminate need for new randomized clinical trial

Sales and marketing

Improve targeting of commercial activities:
- Target underdiagnosed patients
- Identify "super responders"
- Identify patients likely to switch or discontinue
- Inform design of patient services/solutions

Refine commercial strategy:
- Shape product positioning
- Understand healthcare-provider (HCP) decision making and impact on outcomes
- Sharpen understanding of influence networks

Build clinical-decision-support systems:
- Provide recommendations at point of care based on predictions of outcomes, risk, or disease progression



Medical

Improve pharmacovigilance:
- Monitor real-world usage for safety and adverse events
- Rapidly create granular view on benefits/risks

Strengthen evidence for differentiation:
- Analyze efficacy in under-studied populations
- Identify subpopulations for which effect outperforms trials

Improve effectiveness of medical affairs:
- Monitor unmet patient need at HCP level

Improve adherence:
- Support personal engagement to drive adherence and capture patient-reported outcomes with digital tools

[3] "Roche receives EU approval of Alecensa (alectinib) for people with previously treated ALK-positive non-small cell lung cancer," Roche, February 21, 2017, roche.com; Solange Peters et al., "Alectinib versus crizotinib in untreated ALK-positive non-small cell lung cancer," *New England Journal of Medicine*, August 31, 2017, Number 377, pp. 829–38; Jessica Davies et al., "Retrospective indirect comparison of Alectinib phase II data vs. ceritinib real-world data in ALK+ NSCLC after progression on crizotinib," poster presented at 2017 European Lung Cancer Conference (ELCC), May 5–8, 2017, Geneva, Switzerland.

[4] "AstraZeneca's CVD-REAL study shows SGLT-2 inhibitors significantly reduced death and hospitalisations for heart failure versus other type-2 diabetes medicines," AstraZeneca, March 19, 2017, astrazeneca.com.

Comparing traditional and advanced real-world evidence analytics

Traditional real-world evidence (RWE) analytics uses descriptive analyses and established matching techniques (such as propensity score matching) to describe real-world use and outcomes, conduct head-to-head drug comparisons, and compare outcomes for two groups of patients who are matched, as in a clinical trial, to be as close as possible to each other on a relatively small set of patient characteristics. It answers questions such as: What kind of patients use therapy X? What is the adherence to therapy Y? What proportion of patients switch from first-line to second-line therapy within a year? In similar patient populations, does drug X lead to better outcomes than drug Y at a population level? These approaches are well established but can be difficult to generalize, as the number of patient variables considered in estimating outcomes is small, and atypical patients often need to be dropped from the sample.

Advanced RWE analytics uses sophisticated data engineering approaches to build large data sets with rich information on thousands of patient variables. Predictive models, machine learning, probabilistic causal models, and unsupervised algorithms are then used to extract deeper insights from these data sets. By "learning" relationships between thousands of patient variables and patient outcomes, the models are able to predict outcomes for a new patient with a unique set of characteristics. Advanced RWE analytics answers questions such as: Which patient subsegments respond best to therapy X? What are the patient characteristics that predict a switch from drug X to drug Y? Which combinations of patient characteristics cause disease progression, and how do an individual patient's characteristics interact with one another? On which indications in a biological pathway is a drug most likely to be effective? What is the risk of a patient having an event within one, three, or five years of visiting their physician? If all patients on drug A switched to drug B, how would patient outcomes change? How would the total cost to the system change?

Leading organizations are already capturing value from advanced RWE through a range of applications including predicting outcomes in type 2 diabetes,[5] predicting findings of an ongoing phase IV cardiovascular trial,[6] and modeling the progression of non-Hodgkin's lymphoma to predict therapy escalation.[7]

We estimate that an average top-20 pharma company that adopted advanced RWE analytics across its whole value chain for in-market and pipeline products could unlock more than $300 million a year over the next three to five years. A typical cost base offers scope to save $100 million in development spending through the optimization of RCT design, the use of RWE studies rather than RCTs in some cases, and the implementation of synthetic trial arms. Cost savings apart, the introduction of advanced RWE analytics could help companies identify new targets for molecules, accelerate time to market, improve formulary position and payer negotiations, and generate stronger evidence of differentiation and benefit/risk balance for in-market products. Our analysis suggests that applying these actions to key assets could generate top-line value of $200 million or more.

[5] J. Pettus, et al., "Rates of hypoglycemia predicted in patients with type 2 diabetes on insulin glargine 300 u/ml versus first- and second-generation basal insulin analogs: The real-world LIGHTNING study," *Diabetes Therapy*, April 2019; Z. Bosnyak, et al., "Predictive modeling of hypoglycemia risk with basal insulin use in type 2 diabetes: Use of machine learning in the LIGHTNING study," *Diabetes Therapy*, April 2019; S.D. Sullivan, et al., "Comparable glycaemic control and hypoglycaemia in adults with type 2 diabetes after initiating insulin glargine 300 units/mL or insulin degludec: The DELIVER Naïve D real-world study," *Diabetes, Obesity and Metabolism*, May 2019.

[6] Elisabetta Patorno, et al., "Using real-world data to predict findings of an ongoing phase IV cardiovascular outcome trial: Cardiovascular safety of linagliptin vs. glimepiride," *Diabetes Care*, June 25, 2019.

[7] Rafiq Ajani, et al., "How a pharma company applied machine learning to patient data," *Harvard Business Review*, October 25, 2018.

Such examples represent only the tip of the iceberg where RWE is concerned. Emerging methodologies—such as generative adversarial networks, federated transfer learning, time-series modeling, and "few-shot" learning—will pave the way to answering novel questions that can't even be formulated today. Explainable AI methods that enable human experts to understand machine-learning models are enhancing transparency and understanding and catalyzing wider adoption. The explosion in data from electronic medical records (EMRs), health claims, "omics," sensors, wearables, social media, commercial customer records, and patient-reported outcomes will prove fertile ground for new insights.

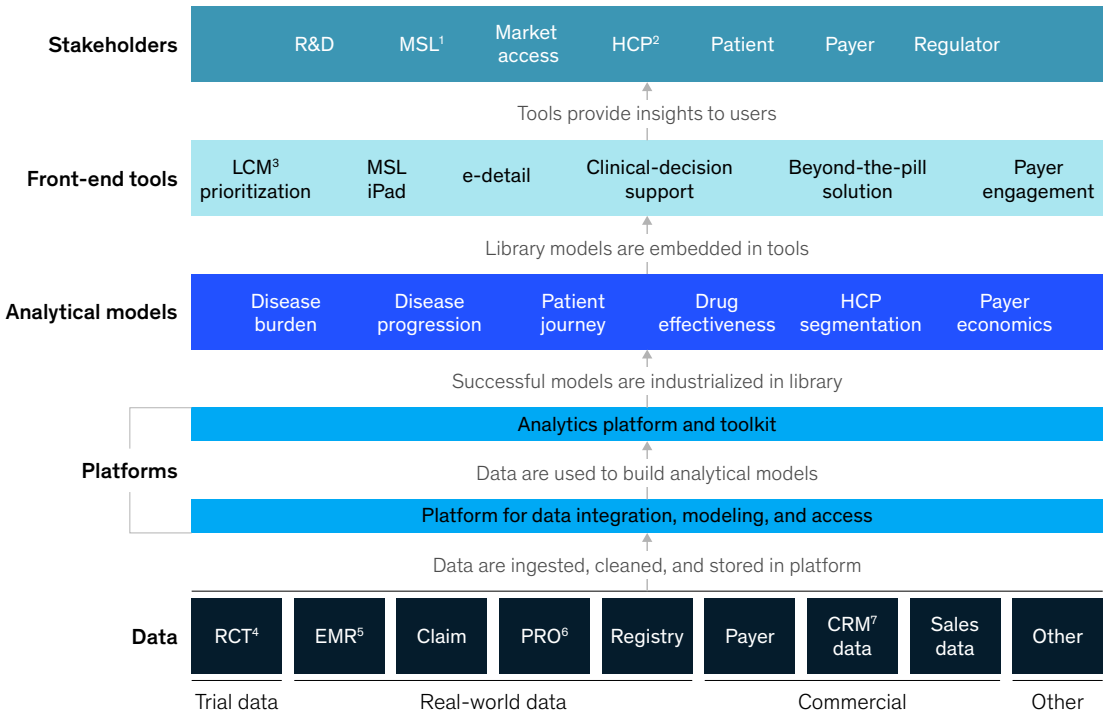
Healthcare companies should also develop a strategy to address disruption from tech giants and payers—signs of which are already emerging. Google's engagement with one of the largest US healthcare systems to collect and analyze data from millions of patients[8] is a sign of growing interest among major companies from outside the sector.

As leading companies deepen their analytics capabilities, they are also scaling up their ambitions beyond one-off use cases for a single brand or market. They are building data pipelines, reusable analytical assets and models, engagement platforms, and ecosystems across groups of mutually reinforcing use cases (Exhibit 2). This approach

Exhibit 2

Advanced analytical models should be built into an enterprise-wide capability stack.

Capability stack, illustrative



[1]Medical-science liaison. [2]Healthcare provider. [3]Life-cycle management. [4]Randomized clinical trial. [5]Electronic medical record. [6]Patient-reported outcome. [7]Customer relationship management.

[8] Rob Copeland, "Google's 'Project Nightingale' gathers personal health data on millions of Americans," *Wall Street Journal*, November 11, 2019.

allows companies to integrate multiple datasets, use them to build analytical models, and then "industrialize" the models for use in a broad range of contexts. Over time, companies can embed the models in user-friendly digital tools for a variety of stakeholders, both internal (R&D, market access, medical science liaisons, and so on) and external (healthcare professionals, payers, patients, and others).

What it takes to deliver

As early adopters invest in building capabilities in advanced RWE analytics, eight dimensions are emerging as particularly important (Exhibit 3). Our research shows that companies need not excel at all eight, but should aim to build a leading position in at least a handful.

Strategy and vision. In best-practice companies, brand and R&D teams work together in a "business-back" way to identify the products and value-chain elements that can benefit most from advanced RWE analytics and specify what value they want to create, how, and by when. Having defined this granular aspiration, they maintain an intense focus on the products and development programs they have targeted and deploy RWE across R&D, regulatory, market access, and commercial activities as well as medical affairs.

Value orientation. After building analytics platforms, pooling data sets, setting up organizations, and defining operating models and processes, some companies have struggled to generate buy-in for advanced RWE analytics from the business. Other companies have had more success by

Exhibit 3

Leaders in advanced real-world evidence analytics get eight things right.

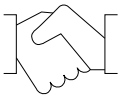
Strategy and vision
Clearly articulated aspiration; link to value; top-down sponsorship; focus along value chain

Value orientation
"Lighthouse" project to demonstrate value and galvanize organization; study design and methods; dissemination; impact tracking

Organization, operating model, and processes
Organizational setup; governance; integration of evidence generation across functions, geographies, value-chain levers, and evidence types

Capabilities
Conventional real-world evidence; epidemiology; health-economics and -outcomes research; advanced analytics; understanding of evidence generation within functions and brands; use of external partners

Culture
Belief in evidence generation; understanding of what it is and isn't; perspective on where it can add value; perception of risks



Partnerships
Innovative start-ups; academic consortia; analytics companies; regulators; payers; providers; patient groups

Data
Long-term partnerships for enrichment, curation, quality control, and governance; classic sources (eg, claims, electronic medical record) and novel sources (eg, -omics,[1] patient-reported outcome)

Tools and environments
Sandboxes for experiments; at-scale pipelines; repositories of analytical assets; "industrialized" evidence-generation engines

[1]Such as genomics, transcriptomics, and proteomics.

following a different approach. To galvanize their organization from the beginning, they execute a "lighthouse" use case that targets an urgent business question and demonstrates the value of RWE analytics in addressing it. Successful lighthouse projects are sponsored by senior leaders, push the boundaries on the use of innovative data and analytics, involve a broad set of stakeholders from across functions, and build enterprise-wide capabilities and reusable assets. By communicating and celebrating such projects internally and externally, companies create demand for RWE analytics from all areas of the business, enabling them to move beyond the lighthouse and drive use cases systematically across the value chain.

Organization, operating model, and processes. To make the most of scarce expertise, best-practice companies set up a global capability group to oversee RWE enterprise strategy, capability building, and governance. They give the group resources to coinvest in pioneering use cases with key brands and centralizing some day-to-day RWE baseload activities. They also incorporate RWE into an integrated evidence-generation process that cuts across functions, asset life-cycle stages, evidence types, methodologies, and global, regional, and country-level needs. In addition, they often create a new role to liaise between RWE and key brands and R&D, charged with identifying opportunities, shaping a portfolio of work, and challenging brands and functions to adopt innovative approaches. The ideal postholder will have business acumen (ideally gained inside the company), brand smarts, medical and analytical knowledge, communication skills, project-management capabilities, an entrepreneurial mindset, and political savvy, plus at least ten years' industry experience across functions.

Capabilities. When companies first introduce advanced RWE analytics, they often get excited about novel modeling approaches and hire a bunch of data scientists. But to deliver at scale, they must also build standardized, reusable data substrates from multiple different sources and design factory-style platforms for handling automated evidence generation—tasks that require them to hire data engineers and machine-learning specialists as well. To inject medical, clinical, epidemiological, and business rigor into every process, they also need "translators" who understand how RWE operates and delivers value.[9] They act as intermediaries between colleagues working in business, scientific, and methodological areas and those working in data engineering and data science, helping to convert business requirements into executable directives for the technical team and interpret the team's outputs into material that business stakeholders can engage with. They also help to ensure integrity, quality, and transparency in a field that has yet to earn the trust that external stakeholders routinely place in registries and RCTs.

Culture. Adopting advanced RWE analytics at scale requires two significant mindset shifts. First, RWE and other post-approval evidence must be treated not as a back-up to evidence generated from RCTs but as a key element in strategic discussions and development programs from the outset. Second, the move from conventional to advanced analytics requires a willingness to go beyond established epidemiological methodologies, adopt novel approaches, and accept a degree of risk in trying new things. Both shifts call for sponsorship from top executives and leadership from managers at all levels with the mandate and conviction to drive change.

Partnerships. Developing the scarce skillsets for delivering innovative RWE analytics can take years. Building long-term partnerships with a small number of analytics companies, designers, academic consortia, and innovative start-ups can offer a faster alternative route to access capabilities. In the most effective partnerships, external

[9] Nicolaus Henke, et al., "Analytics translator: The new must-have role," *Harvard Business Review*, February 2018.

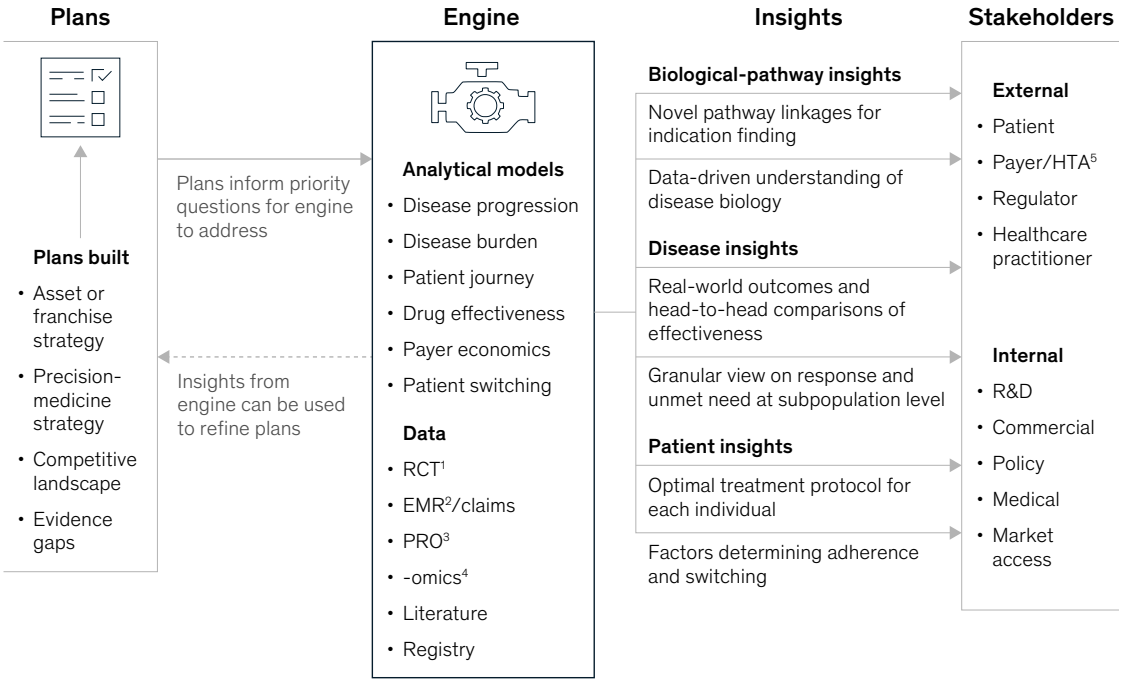
specialists don't simply do the work and hand over deliverables but are offered incentives to build capabilities inside the pharma company's organization. To help shape thinking and advance the field, pharma companies also need to engage stakeholders including regulators, payers, health technology assessment (HTA) bodies, healthcare providers, and patients.

Data. Building a network of relationships with carefully chosen data providers helps pharma companies secure privileged access to data and develop proprietary enriched data sets to answer business-critical questions about key assets. To do this, companies scan multiple market landscapes to identify emerging data generators and aggregators, develop a clear process for acquiring and accessing data, and adapt their enterprise governance to support collaboration. Some companies are starting to link RWE datasets with their own data while reanalyzing their RCT data in parallel to build a comprehensive yet granular view of the effectiveness and safety of their therapies.

Tools and environments. At a minimum, companies that aspire to scale up their RWE analytics need a "sandbox" for conducting basic experiments with use cases and delivery models. More advanced companies use scaled-up cloud platforms to build automated pipelines, repositories of analytical assets, and visualizations for use by multiple stakeholder groups. A few companies go further still by building platforms that generate evidence across indications, therapies, and use cases and allow hundreds of analyses to be run across multiple patient outcomes and thousands of sub-populations. These evidence-generation engines deploy advanced and traditional RWE analytics side by side to derive insights into disease biology, unmet needs, real-world therapy usage, safety and effectiveness, drivers of healthcare professionals' choices, and other factors to inform decision making (Exhibit 4).

Exhibit 4

Creating value at scale requires an evidence-generation engine.



[1]Randomized clinical trial. [2]Electronic medical record. [3]Patient-reported outcome. [4]Such as genomics, transcriptomics, and proteomics. [5]Health-technology assessment.

The evidence generated in this way is also used in head-to-head comparisons of effectiveness and safety, cost-effectiveness analyses to support submissions to payers and regulators, and other forms of communication with external stakeholders. Last but by no means least, evidence from the engines can be used to improve patient outcomes. Predictive models of patient-level outcomes can be used in clinical decision support, for example, while segmentation can be used to get the right drug to the right patient at the right time.

In combination with tech-enabled planning to integrate evidence generation across functions and brands, these engines will transform RWE from a source of insights for medical affairs to a pillar of corporate strategy and a key part of the value chain. Companies that lack this vision could struggle to compete with others that are able to base their decisions on richer insights generated at a fraction of the usual time and cost.

By taking full advantage of real-world evidence and advanced analytics, pharma companies can accelerate their shift from product-focused to patient-focused organizations. A few leaders have drawn up a blueprint for execution. Now it is time for the rest of the industry to set its sights on the next horizon of evidence-generation capabilities.

David Champagne is a partner in McKinsey's London office, where **Alex Davidson** is an associate partner and **David Saunders** is a consultant, and **Lucy Pérez** is a senior partner in the Boston office.

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