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Real-world evidence: From activity to impact

Insights into Pharmaceuticals and Medical Products

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Real-world evidence: From activity to impact

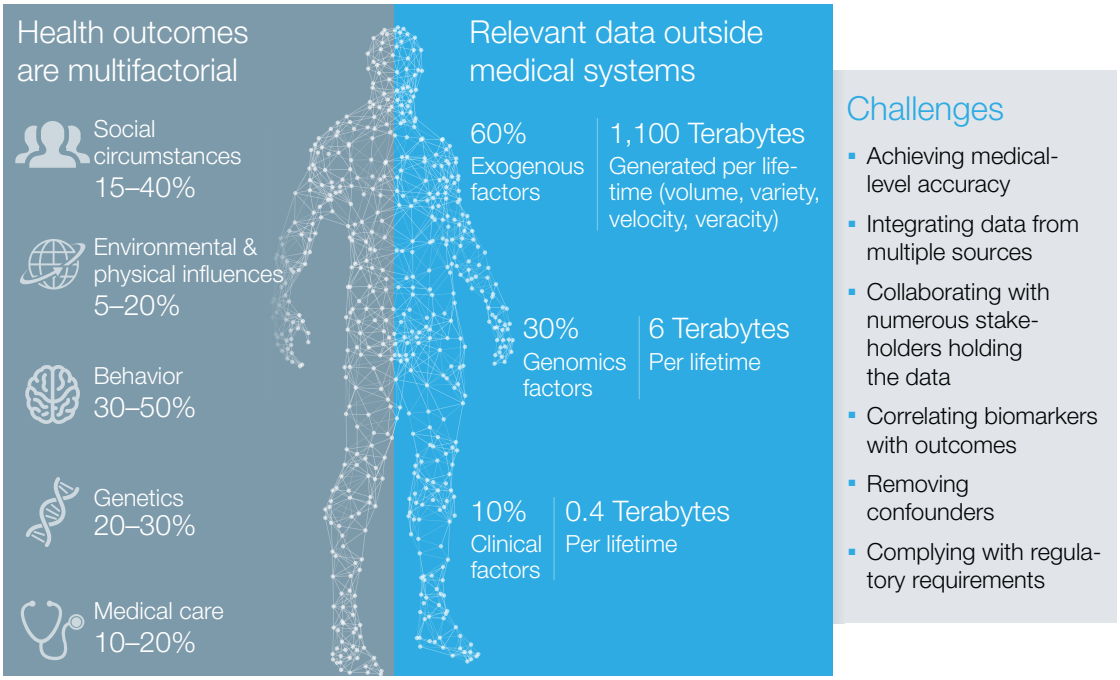
While there is general agreement that real-world evidence could significantly improve healthcare decision making, expanding its use requires action by multiple stakeholders.

Healthcare is rapidly transitioning to a new world of patient choice with a laser-like focus on outcomes and value. Indeed, healthcare systems that have traditionally focused on medical interventions driven via episodic interaction with the patient are now recognizing the need to fully understand exogenous factors and deliver continual care.

Exogenous factors such as genomics, behavior, and social and environmental influences play a critical role in delivering outcomes and value for patients and health systems; meanwhile, technology is finally allowing the capture and analysis of such real-world data (Exhibit 1).

Exhibit 1

Envision a holistic approach to healthcare where all relevant data shapes decisions real time



Researchers from the US Food and Drug Administration (FDA) define real-world evidence (RWE) as: "Healthcare information derived from multiple sources outside of typical clinical research settings, including electronic medical records (EMRs), claims and billing data, product and disease registries,

and data gathered by personal devices and health applications." They acknowledge that these datasets can "effectively complement the knowledge gained from "traditional" clinical trials, whose well-known limitations make it difficult to generalize findings to larger, more inclusive populations of patients, providers, and healthcare delivery systems or settings reflective of actual use in practice."[1]

Real-world data traditionally comes from four sources—clinical data, administrative/claims data, patient-generated/reported data, and emerging data sources including social media and cross-industry data collaborations such as Project Data Sphere (see sidebar "The ever-expanding trove of real-world data").

The ever-expanding trove of real-world data

Real-world data sources generally fall into four categories (although these could expand in the future):

Clinical data

These are patient-level data pulled from electronic medical records (EMR) and patient registries that describe how patients are treated in the real world. They include lab values, diagnoses, notes, and other information from healthcare visits with physicians and other care providers. With more data from hospitals and entire health systems becoming digitized and more easily integrated across institutions, the power of these particularly rich datasets (for example, larger sample sizes, easier comparisons across systems) is increasing.

Administrative/claims data

Detailed patient-level data is also collected for non-clinical purposes, primarily for billing by providers to insurers and other payors, which can include diagnoses, services provided, costs, and other data required for the reimbursement of healthcare services. Other more administrative sources of data can also include data collected for tracking purposes, such as patient or population surveys.

Patient-generated/reported data

This category covers individual data describing the patient's experience and is typically both collected and shared/reported by the patient. Today this source of data is less prevalent than others but will likely expand due to the increased use of wearable devices that automate data collection and sharing. Online communities such as PatientsLikeMe encourage and enable sharing of patient-generated data with peers and investigators.

Non-traditional, health-related digital data sources

As digital becomes increasingly prevalent in our lives, new sources of patient-level health data are emerging. These span social media posts that have a rich trove of information, especially health-focused social media sites like Sage Bionetworks. Project Data Sphere is a pharmaceutical industry-sponsored platform to share, integrate, and analyze phase III comparator arm data from cancer trials to accelerate research.

1 U.S. Food and Drug Administration, "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices," August 31, 2017, https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf.

The data environment continues to mature rapidly, with public-sector organizations, not-for-profit organizations, and commercial entities compiling expansive data pools. A number of developed countries have accumulated large datasets containing information about several hundred million patients (Exhibit 2). In parallel, large corporations such as IBM and IMSQuintiles are offering rich data sets of their own. Unstructured data are starting to yield interesting insights as well. Online communities such as PatientsLikeMe afford unique views of patients managing their conditions in real time. Recently, Microsoft collaborated on an effort to extract insights from analysis of search records to predict pancreatic cancer.[2] Retroactive analysis of search content (such as symptoms) were found to clearly identify 5–15 percent of the undiagnosed population several months before a formal diagnosis was made. For this deadly condition, those months can make a huge difference.

Exhibit 2

Sample high-value real-world data pools in prioritized countries

	Database[1]		Lives covered, Millions	Industry access
Japan	MHLW	National claims database	126	Possible through academics, often requires significant data cleaning
US	CMS	Medicaid/Medicare claims databases	120	Possible through academics, but with limitations
France	SNIIRAM	National claims database	60	None, limited to academics and health policy experts only
	PMSI	National hospital claims database	60	Through academics only, but future unclear due to privacy concerns
UK	CPRD	Electronic medical record (EMR) data from 10% GPs	53	Open, 80% of pharma companies purchase access to raw data
	HES	English hospital EMR database	15	None, raw data previously available before "care.data" concerns
Germany	AOK, WIdO	Regional public sickness funds claims data	24	Possible through academics but long wait times and reluctant to share with industry
	Barmer GEK		9	
	TK, Wineg		7	
Denmark	sundhed.dk	National cross-linked healthcare databases	6	Possible through academics, but time consuming

1 CPRD (Clinical Practice Research Datalink), HES (Hospital Episode Statistics), MHLW (Ministry of Health, Labour, and Welfare), PMSI (Le Programme de médicalisation des systèmes d'information), SNIIRAM (Système National d'Informations Inter Régimes de l'Assurance Maladie), WIdO (Wissenschaftliches Institut der AOK).

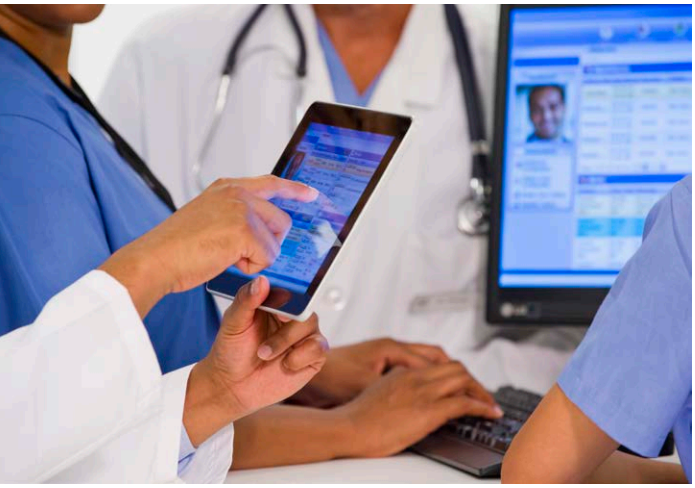
Source: Interviews with industry and other thought leaders; press releases; publications; websites

2 John Paparrizos, et al., "Screening for pancreatic adenocarcinoma using signals from web search logs: Feasibility study and results," *Journal of Oncology Practice*, June 2016, http://ascopubs.org/doi/full/10.1200/JOP.2015.010504.

Healthcare stakeholders are responding rapidly

The importance of real-world data continues to touch all areas of our lives, with stakeholders across the entire healthcare value chain—physicians, providers, payors, regulatory bodies, and pharmaceutical and medical device manufacturers—using real-world evidence to guide their decisions.

Physicians and providers rely on electronic medical records (EMR) data for physician-led clinical research while health system administrators use the same data to monitor the quality of care delivered across the system, including monitoring adherence to care pathways. Historically, many physicians have carried out chart reviews of their own patient populations, but with the growth of EMR, physicians can now quickly access the same data across a larger number of patients and institutions—an innovation that has transformed the impact of physician-led research. In the United States, consolidation of hospitals and healthcare systems has resulted in a larger scale of operations that in turn centralizes control over prescribing and requires a sharper focus on value as a consequence of risk-bearing contracts. The United Kingdom is ahead of the trend, with the National Health Service already imposing value-based pricing for some therapies. For example, the NHS recently negotiated an arrangement with Janssen related to the use of Olysio (a Hepatitis C therapy) under which the NHS receives a rebate if patients are not cured after 12 weeks of treatment.[3] To improve results, Janssen offers pre-treatment blood tests to identify patients who might not respond to the treatment.



Payors are analyzing their claims data to improve affordability of healthcare for members, and frequently integrate claims with EMR data to generate insights into the value and effectiveness of providers or protocols. More US payors are using outcomes-based contracts with providers: an estimated 80 percent of physicians and 100 percent of hospitals now have at least one such contract, and the percentage of payments that are value-based are estimated to have doubled from 10–15 percent in 2013 to 25–35 percent in 2014.[4] In Europe, health technology assessments are used to compare treatment patterns with National Institute for Health and Care Excellence (NICE) guidelines, and inform pricing and reimbursement levels. The UK's Systemic Anti-Cancer Therapy Chemotherapy dataset (SACT) was established in 2011 to document therapy across the United

3 Eric Palmer, "Janssen agrees to rebate cost of Olysio to England's NHS if it doesn't work," *FiercePharma*, January 16, 2015, http://www.fiercepharma.com/pharma/janssen-agrees-to-rebate-cost-of-olysio-to-england-s-nhs-if-it-doesn-t-work.

4 Statistics derived from the following sources: Availity, Catalyst for Payment Reform, CMS, Health Affairs, MedScape.

Kingdom, support treatment choices, and gain better insight into service provision and treatment patterns.[5]

However, when it comes to pharmacy costs, payors are still under immense pressure and continue to rely on traditional levers such as formulary status, co-pays, step edits, and prior authorizations to manage costs. Yet there has been movement recently with companies starting to enter into value-based partnerships with payors that link the net price of drug to expected outcomes. That said, while innovative contracts are growing in importance, they are not yet widespread.

Regulators use RWE to monitor the safety of marketed products through traditional pharmacovigilance tools (for instance, Periodic Benefit-Risk Evaluation Report, Periodic Safety Update Report, and Vaccine Adverse Event Reporting System) as well as newer digital aids such as the FDA Sentinel Initiative, a post-market active safety surveillance system.[6] Pre-approved use of RWE in efficacy decisions occurs today and there is potential for it to be used more broadly, such as in oncology, rare diseases, and pediatric conditions when randomized controlled clinical trials are impossible or unethical to conduct.[7] In parallel, legislators are recognizing the value of RWE. In the United States, the 21st Century Cures Act passed in December 2016 establishes public-private partnerships to collect data and improve understanding of diseases, supports patient-focused drug development, and modernizes the design of clinical trials and their review process.

There is an emerging desire by regulators to make RWE much more central to their activities. This is reflected in the FDA's efforts to integrate data collected from electronic medical records, claims data, and registries to create a unified system for monitoring the safety of medical products. Similarly, a National Institutes of Health (NIH) Common Fund has been established to build infrastructure, operational knowledge, and capacity for "pragmatic research" that incorporates electronic health records and other real-world data into large-scale distributed research networks to allow researchers to identify cohorts of interest more easily and expedite studies.[8]

Pharmaceutical companies have rapidly progressed in their use of real-world evidence. Generation I (circa 2011) had limited use of RWE and was heavily focused on safety and post-market. Generation II (2011–15) saw more integrated use of RWE across the end-to-end product

5 Leela Barham, "Real-world evidence for pricing and reimbursement: the potential of Systemic Anti-Cancer Therapy (SACT) data," *Pharmaphorum*, January 15, 2015, http://pharmaphorum.com/articles/real-world-evidence-for-pricing-and-reimbursement-the-potential-of-systemic-anti-cancer-therapy-sact-data/.

6 *Sentinel Initiative Final Assessment Report*, September 2017, https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM577502.pdf.

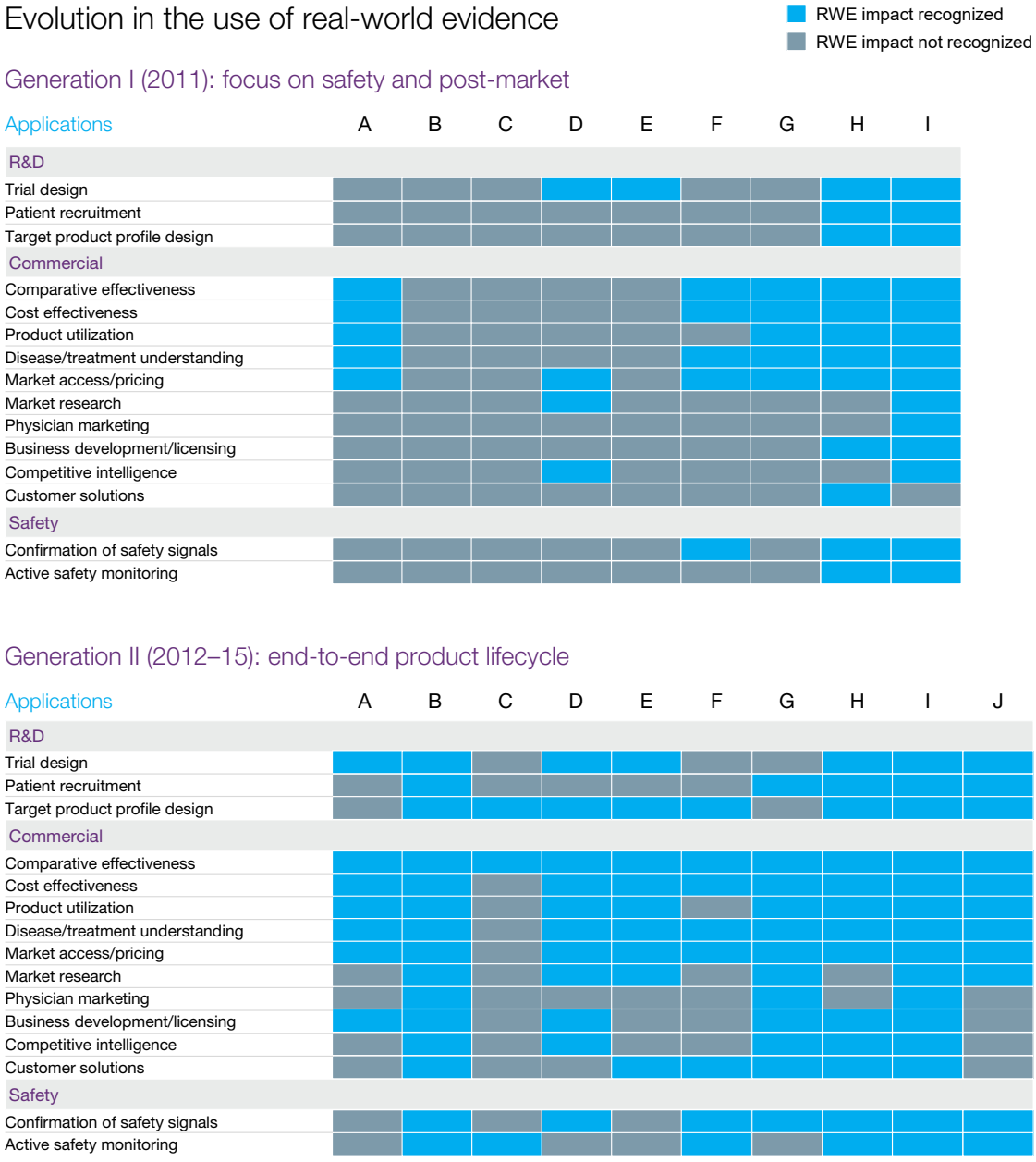
7 U.S. Food and Drug Administration, "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices," August 31, 2017, https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf; Scott Gottlieb, MD, "Advancing Public Health Opportunities with Real World Evidence," National Academy of Sciences, September 19, 2017, https://www.fda.gov/NewsEvents/Speeches/ucm576519.htm; Rachel E. Sherman, MD, MPH, et al, "Real-World Evidence — What Is It and What Can It Tell Us?," *The New England Journal of Medicine*, December 8, 2016, http://www.nejm.org/doi/full/10.1056/NEJMsb1609216.

8 National Institutes of Health, Healthcare Systems Research Collaboratory, "About us," https://www.nihcollaboratory.org/about-us/Pages/default.aspx. Accessed September 15, 2016.

lifecycle during which it was deployed to support regulatory decisions, advance disease understanding and clinical guidelines, and support outcome-based reimbursement decisions (Exhibit 3).

Exhibit 3

Evolution in the use of real-world evidence



Source: McKinsey RWE benchmarking 2011 and 2013

In general, evolving RWE strategies over the past two to three years reflect companies' increasing recognition of the importance of these capabilities. Their efforts have been translated into organizational changes with the real-world evidence function becoming more centralized as companies seek to elevate standards and quality.

Today, we see a greater focus on the insights derived from real-world data, as well as recognition of the impact these can have on improving decision making and patient care both internally and by regulators, physicians, and payors (Exhibit 4). Indeed, the senior leadership in many pharmaceutical companies has invested in and built out centralized RWE capabilities around data acquisition, standards, and processes. Typically, these centralized teams sit in global medical affairs to promote the cultivation of more robust RWE science and support a broader vision for the real-world evidence function (Exhibit 5). That said, RWE capabilities around study design and management are more likely to remain scattered across the organization; this creates a challenge for RWE leaders to make a case for RWE with line leadership as compared with other, more traditional approaches to evidence generation (such as randomized controlled trials). Top talent engaged in RWE activity is broadly recognized as the key differentiating factor of leading RWE organizations—these organizations need people with deep knowledge of real-world data and analytics, business leaders with strategic vision, and communication skills to make a case for real-world evidence across the organization and externally.

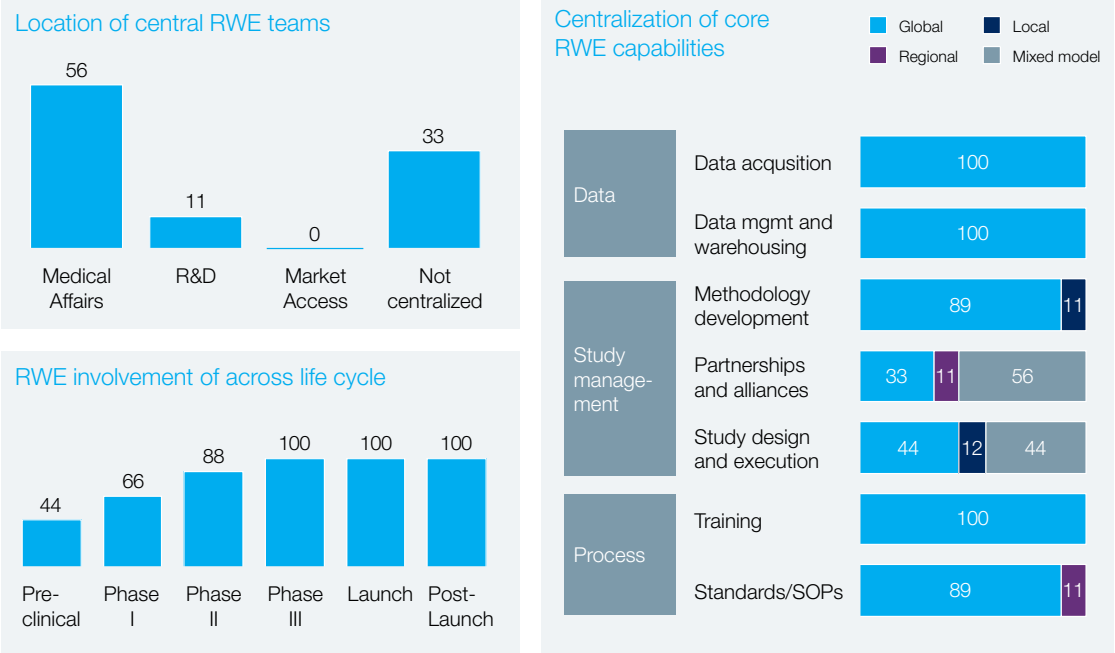
Exhibit 4

Three generations of real-world evidence
Generation III (2016): Focus on insight and impact

Exhibit 5

Approaches to centralization of RWE teams

% of companies



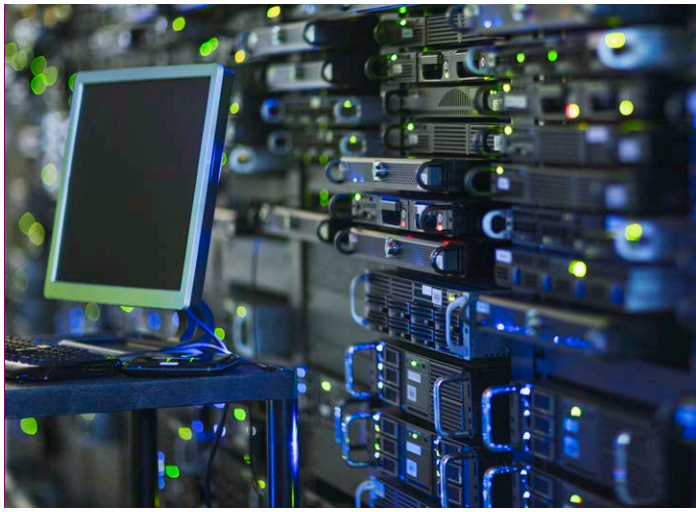
Source: McKinsey RWE Benchmarking (2017)

Barriers to increased use of real-world data

Among the most significant barriers to expanding use of real-world data is the consensus that randomized controlled trials (RCT) remain the gold standard for demonstrating the efficacy and safety of medical products and treatments. This consensus, shared by physicians, patients, payors, and regulators alike, creates significant hurdles to using RWE, even though there is a growing recognition that RCT alone cannot provide sufficient data for informed healthcare decision making in some situations. Because RWE can capture the use of medical treatments in real-life settings it could be used to better understand and characterize patients, and evaluate new treatments when randomization to placebo for clinical trials may be impossible, impractical, or unethical. In addition to the preference for RCT, other barriers to developing and using RWE exist and need to be addressed to realize the potential of this data source.

Uneven quality of real-world data sources

Valuable real-world data exists in many countries, although it is most prevalent in the United States and Europe. Policies promoting collection of real-world data vary widely even within these regions, a reality that significantly impacts the quality of data, with data fragmentation remaining a major challenge. Some countries—such as those in the Nordic region—have developed rich databases cross-linking a patient's health data with other national databases, but these datasets reflect relatively low national populations. Bigger countries, such as France and Germany, have built large national databases covering millions of lives but generally these are narrowly focused on the claims data required to manage their healthcare system. It is critical to have policies and incentives in place to promote data capture by physicians and high-quality inputs into the database, especially in countries with nationalized healthcare systems, in order to build a database that can also be used for scientific research into public health.



Limits to access to real-world data

More uniform access to existing real-world databases for medical research could improve data quality. However, there is not consensus among patients, physicians, politicians, and the general public regarding the potential public health benefits of real-world data. Privacy concerns related to allowing access to these large datasets and the potential results of advanced RWE analytics have restricted both the collection and sharing of existing data. Although there is stronger support for access by independent academic research (in comparison with industry-sponsored science), data access remains one of the primary hurdles to advancing the science of RWE analytics.

Lack of standardization of RWE analytics

Despite the potential value of real-world data, it is also clear that a lack of standardized methodologies to develop RWE undercuts its broader use. Unlike RCT methodologies and practices (for example, Good Clinical Practices [GCP], and other practice quality guidelines), which are well developed and understood, the same cannot be said for RWE. Poor-quality analyses, limited transparency into methods, and bias in results are just a few of the issues that a lack of standardization brings. Rigorous, yet practical, methods and practices are needed to define how collecting, analyzing, and reporting real-world data should be done. Today, many RWE analytics are retrospective or observational—both of which are problematic. To be influential and useful, real-world data needs to be susceptible to robust analytics to confirm that data methods have eliminated biases, controlled quality, and allowed for integration of disparate data sources for both prospective and retrospective studies. Greater transparency around RWE study design and results is needed, similar to the publication of other pharmaceutical company studies through clinicaltrials.gov.

Varied public support for RWE

Even if the technical aspects of using real-world data ethically and responsibly for the benefit of public health are resolved, there remains a huge education task to convince stakeholders that the benefits of real-world data collection and analyses outweigh the risks of sharing such personal information. Some countries—for instance, Denmark—are having public discussions about developing a national health database; while, in the United Kingdom, general practitioner concerns about privacy and accountability are stalling the rollout of a real-world data platform. No country has resolved all the issues, but lessons can be drawn from current discussions to shape future policies.

While real, all these barriers can be overcome with concerted effort by stakeholders, particularly if stakeholders collaborate to advance RWE in partnership with data providers.

Signs of growing acceptance of real-world evidence

Despite these hurdles, we see growing use of real-world datasets within a narrow set of circumstances. As detailed above, RWE is used most commonly by pharmaceutical companies, payors, and providers to better manage their organizations and make decisions about cost-effectiveness and comparative efficacy where other more robust data sources do not exist. Today, real-world data may sometimes be the best available source of safety data for on-market products as demonstrated by the preference of payors for their own data over clinical trial data, and by the FDA's Sentinel Initiative which uses claims and EMR data from many different databases to characterize and study potential safety risks of marketed products.

Even so, realizing the vast public health benefits of these datasets will require broader use of this type of data. Real-world evidence can play a greater role in assessing efficacy, especially in situations where randomized controlled trials do not or cannot provide the data needed. However, large-scale expansion hinges on regulatory-approved approaches to RWE analytics. There are also some early signs that RWE is starting to be accepted by regulators, physicians, and patients for benefit decisions. Notably, this is occurring in a small subset of rare disease areas, such as oncology, orphan diseases, and similar therapeutic areas. Situations that support RWE are typically characterized by a lack of other therapeutic options, where the condition is seen as a life-threatening disease, where it affects a small population size, and/or the effect is easily measured. As RWE becomes increasingly accepted, we expect to see situations which meet some but not all these criteria supporting the use of RWE (see sidebar "Emerging regulatory use cases for real-world evidence in benefit assessment").

Incorporating RWE as an integral component of the data package on a product across the lifecycle (for example, from proof of concept to loss of exclusivity) would increase the knowledge of all stakeholders regarding potential benefits and side effects. With more robust data, improved methodology, and greater clarity about regulatory frameworks, RWE analytics in the short term could support:

- Therapeutic effectiveness, for instance by suggesting new and effective benefits for new products or for additional indications, assessing the optimal doses of approved products
- Understanding special populations that could benefit from a product, including protected populations such as the elderly, pregnant, or pediatric patients, while also enabling better understanding of effectiveness in patient sub-populations
- Fulfilling post-marketing requirements—for example, committing to RWE analytics after approval to further understand product benefit
- Enhancing the label to better inform patients and healthcare practitioners of important information not included in approved indication (such as adding benefit/risk information from observational studies)

Emerging regulatory use cases for real-world evidence in benefit assessment

Looking forward we see five use cases emerging for using real-world evidence in the benefit assessment by regulators.[7 (p 19)] Companies are just starting to include RWE in regulator submission packages that meet the following criteria.

1. **RWE used to establish historical controls.** When patients cannot be randomized to placebo such as in life-threatening orphan diseases with no adequate therapeutic options, historical controls are needed. Before the advent of EMR, physicians would physically scour old patient charts to build historical controls for regulatory submissions. Now with the advent of electronic medical records, this patient-level data can be assessed on a larger number of patients more easily and effectively.
2. **Early approval with RWE post-market monitoring.** In these cases, drugs for life-threatening diseases without adequate treatment options would be approved based on strong early clinical evidence (for example, approval based on only phase II or III randomized clinical trial) and be required to complete post-market monitoring via RWE only. In these disease states, some companies have struggled to recruit sufficient numbers of patients within a reasonable time frame to meet regulatory requirements for post-market randomized controlled trials; suggesting that RWE analytics may be a better approach in some cases.
3. **On-label RWE from another country submitted.** These are cases where a drug has already been approved outside the United States. For example, after an initial rejection for an expanded indication, NovoSeven was approved for those indications based on RWE collected through registries located primarily in Europe and Canada.[9]
4. **Medically accepted alternative-use RWE submitted for new indications.** Electronic medical records can contain rich data on drugs being used off-label for medically accepted alternative uses (for instance, based on recommendations in clinical guidelines developed by physicians). Today, this data has been included in a handful of successful regulatory submissions, but this is likely to increase.
5. **Medically accepted alternative-use RWE submitted for expanded populations.** Similar to RWE supporting use for new indications, electronic medical records contain rich data on drugs being used off-label for new populations (for instance, those not included in initial approval such as children, pregnant women, and also disease sub-populations such as patients with less severe disease). RWE was the sole data source evaluated by the FDA for the approval of the Sapiens transcatheter heart valve for an expanded patient population.[10]

9 Novo Nordisk, "FDA Approves NovoSeven® RT for the Treatment of Glanzmann's Thrombasthenia (GT) With Refractoriness," July 7, 2014.
10 Jeffrey Shuren, MD, JD, and Bram Zuckerman, MD, "How Creative FDA Regulation Led to First-in-the-World Approval of a Cutting-Edge Heart Valve," *FDA Voice*, June 14, 2017.

Next steps

Real-world evidence could significantly improve healthcare decisions across the health system and ultimately improve patient care. Expanding its use, however, will require multi-stakeholder action on several priorities, as well as company-specific campaigns. The broad healthcare community is best equipped to make progress on the following goals:

1. **Increasing understanding and communication of RWE value drivers while focusing on high-impact use cases.** RWE analytics delivers valuable information, which frontline staff are responsible for getting, into the hands of payors, healthcare providers, and regulators to improve their healthcare decision making. A significant elevation of frontline capabilities across medical affairs, commercial, development, and health economics and outcomes (HEOR) will be required to share these analytics in a compliant and impactful fashion.

2. **Creating an operating model that drives integration and adoption of RWE and manages risk.** This should include coordinated funding linked to milestones, an integrated evidence plan, and a governance process to manage risk from RWE activities. An integrated evidence plan (IEP) can link CDT/GCT, regions, and countries which clarifies collaboration and establishes a dossier. Accountable directly to GOC to oversee RWE operating model, RWE leaders will need to establish processes to manage risk especially in small countries and across functions (for example, commercial) as this output is typically not included in the product label, yet may be critical information for physicians, patients, payors, and others to improve healthcare decisions and patient outcomes. Additionally, an “Early Patient Insight and Value Output Team” (led by a DAS commercial leader) can coordinate across stakeholders and regions to uncover insights and architect solutions. RWE leaders must ensure the appropriate mix of non-interventional studies, and build internal capabilities across multiple study designs to improve internal decision making. Ultimately, RWE leaders are needed who can develop a RWE strategy, lead the execution of a RWE study, and communicate the outputs across the entire range of non-interventional studies being carried out internally and externally.

3. **Shaping an integrated, adaptive partner ecosystem.** Companies will need to identify academic collaborations to ensure credibility and trust in analyses, as well as gain access to novel data sources. Unbiased academic experts are needed to address short-term concerns around credibility and trust of these analytics. Companies may also need to consider partnerships with subject matter experts that have defined roles, such as in analytics. In the long term, investment in building RWE expertise across the entire healthcare industry will be needed to elevate the science and methodology of RWE analytics so that it is on par or even better than RCT in specific situations. Similarly, partnerships with database owners will be required in the short term to use data in restricted access databases, especially large, government-funded databases of public health systems in Europe which typically restrict access to this data. In the long term, however, such partnerships could demonstrate the public-health benefits of RWE to both database owners and the public at large to build support for higher-quality real-world databases and expanded access to them.

4. **Building platforms at scale to manage and analyze data in a rapid, low-cost fashion.** RWE leaders must simultaneously capitalize on the benefits of RWE over RCT and address the inherent weaknesses of real-world data sets. Building platforms and capabilities—including data infrastructure and storage—to increase the turnaround time and decrease the cost of RWE studies is critical to being able to utilize this data for internal business decisions. Platforms can also incorporate standardized methodology, which can be applied across all studies, improving the robustness and credibility of outputs.

Making progress on these goals will establish the kind of culture where RWE innovation will flourish, while ensuring that necessary, complementary capabilities exist to support both traditional R&D activities focused on clinical trials and RWE research.

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