COVID-19 OPENS A NEW ERA FOR REAL-WORLD EVIDENCE IN PHARMA

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THE COVID-19 CRISIS PRESENTS an inflection point for the use of real-world evidence (RWE) in the pharmaceutical industry. The pandemic has triggered an unprecedented race to produce safe and effective therapies and vaccines. The desire to drastically accelerate research and development, reinforced by a greater understanding of data science, has made the health care community more receptive to expanding the use of RWE beyond traditional safety-related applications.

But several notable stumbles have occurred in the sprint to apply RWE during the urgency of the pandemic. These problematic clinical studies have highlighted limitations relating to inadequate data and methodologies and the lack of epidemiological expertise among data scientists. The problems have also drawn attention to the fact that health authorities have not yet issued RWE methodology guidelines and standards. Researchers could have used these to improve their studies or identify flaws much earlier.

Despite the challenges, RWE studies—when done right—can create significant value throughout the product life cycle. To succeed, companies must first set a strategy that is grounded in a strong understanding of which therapeutic areas and products to prioritize and must define specific RWE applications that will complement conventional clinical studies. With a strategy in hand, organizations can adopt a fit-for-purpose approach. Equally important, now is the time for pharma firms and health authorities to accelerate and strengthen ongoing efforts to define and enforce RWE standards.

Promising Opportunities but Dangerous Pitfalls

RWE is clinical evidence, derived from real-world data, regarding a medical product's usage and potential benefits and risks. Data sources include electronic health records (EHRs), claims and billing, product and disease registries, patient-reported information, and personal devices and health applications.

In recent years, pharma companies have increasingly recognized the value of RWE for augmenting traditional clinical studies, extending its use beyond the usual pharmacoepidemiologic safety. Additionally, patient associations and legislators have advocated for RWE, while regulators are progressively encouraging new applications. For instance, the 21st Century Cures Act, enacted in the US in 2016, opened the door for RWE use in label extension. And both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have published frameworks to advance the use of RWE in the coming years.

In the urgency of the pandemic, researchers have drawn on RWE to study the use of existing drugs to treat COVID-19. But generating reliable RWE has been difficult owing to the novelty of the virus. For example, as testing and diagnostics have ramped up, the reported number of cases and deaths across countries and over time has been inconsistent, which has made it challenging to understand and compare fatality rates. The result has been more controversies than should be expected from RWE studies.

Hydroxychloroquine is the most prominent example. In Marseille, France, the IHU Méditerranée Infection—in the context of intense media coverage—studied the use of hydroxychloroquine combined with azithromycin (AZT) to treat a cohort of 1,061 COVID-19 patients. It concluded that the observed death rate of 0.5% was proof of the treatment's efficacy. But the study did not use a randomized approach with a control group.

This flaw became apparent after a separate study by the University of Oxford demonstrated that age is the strongest predictor of mortality, by a factor of 50 in COVID-19 patients older than 65 compared with those 65 or younger. Because the patient cohort's average age in the IHU study was only 43.6, the low death rate likely indicated that the immune system of relatively young patients was doing its job, rather than demonstrating the treatment's efficacy.

In another example, the *Lancet* was forced to retract a retrospective study on the adverse effects of hydroxychloroquine. The researchers had mixed EHRs from inconsistent sources, compromising the overall quality of the combined data set.

But some RWE studies have generated reliable results. For example, Epi-Phare, a French research organization, compared how patients taking hydroxychloroquine to treat autoimmune diseases fared against the general population with regard to the risk of hospitalization, intubation, and death related to COVID-19. Adjusting for the higher pathological risk in those patients, the study found similar outcomes compared with the general population—indicating the absence of preventive protection.

Applications for RWE Across the Product Life Cycle

Pharma companies should not steer away from using RWE because of the problems encountered by some studies in the midst of the pandemic. In fact, as regulators have shown greater interest in faster and more cost-effective drug development, the current environment has created additional opportunities to augment and complement traditional clinical studies with RWE, both during development and after launch.

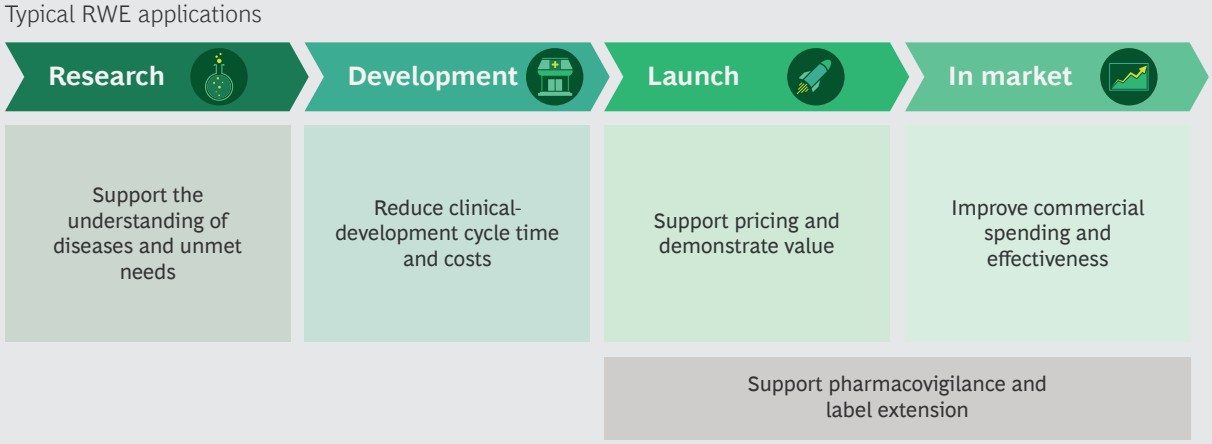
To help pharma companies understand the opportunities, BCG has grouped the applications for RWE along the product life cycle into five categories. (See Exhibit 1.)

Support the Understanding of Diseases and Unmet Needs

RWE is well suited to observational studies conducted to support primary market research. Pharma companies can use RWE throughout the product life cycle to:

- Understand diseases and biological pathways—including how the target population is being treated, patient characteristics, diagnostic markers, and disease progression
- Identify the current standard of care

EXHIBIT 1 | Real-World Evidence Is Valuable Across the Product Life Cycle



Source: BCG.

and associated unmet needs—especially for rare diseases

- Generate hypotheses, through the application of advanced analytics, for how to extend current product use—for example, new indications, new target populations, and combination therapies

Reduce Clinical-Development Cycle Time and Costs

Pharma companies are increasingly using RWE to shorten the clinical-development cycle and decrease its costs. For example, innovative trial designs leverage hybrid or virtual control arms to cut the number of patients receiving placebo, resulting in faster outcomes. RWE is particularly well suited in cases where using a control arm is unethical or infeasible (such as for rare diseases or in oncology) and when preliminary data indicates that a drug's effect could be significant compared with the current standard of care.

Additionally, pharma companies can gain speed and cost advantages by using RWE to:

- Optimize site selection and patient recruitment with predictions of clinical outcomes based on selected trial criteria and sites' past performance

- Augment clinical trials, such as demonstrating the impact from the patient's standpoint—for example, using wearables to assess how a drug affects quality of life

- Refine their assessment of a clinical trial's probability of success on the basis of preliminary results, allowing for the early termination of an unsuccessful trial

In several cases, regulators have accepted the use of RWE to support drug approvals. For instance, in 2014, the FDA accelerated the approval of Amgen's leukemia drug Blincyto (blinatumomab) after evidence from a single-arm trial showed complete and sustained remission. The study compared the response rate in the trial with historical real-world data from 694 comparable patients, extracted from their patient records. In most cases, regulators have required further study in a randomized controlled trial (RCT) to verify clinical benefit following approval.

Support Pricing and Demonstrate Value

Pharma companies can use RWE to complement traditional RCT data in order to:

- Demonstrate the value of a new drug to patients, payers, key opinion leaders, and health care providers—for example, RWE can support payers in comparing a therapeutic with the current standard of care, such as with respect to comfort and side effects

- Facilitate the use of value-based contracts with payers—typically for high-cost drugs, such as personalized therapies

Payers regard prospective observational studies as the most robust use of RWE, but such studies require a long-term investment. Patient registries and databases can also provide useful information to support a payer's decision on whether to cover a treatment. Local registries are required when outcomes are closely linked to a country's health care environment.

Going forward, RWE could be used to reduce the cost of expensive personalized therapies. For example, for certain rare diseases, payers could use RWE for measuring outcomes in a value-based contract. In the US, the Prescription Drug Pricing Reduction Act of 2019, approved by the Senate Finance Committee but now stalled in Congress, includes a provision for Medicaid to pay for new gene therapies over time according to measurements of real-world outcomes.

Improve Commercial Spending and Effectiveness

Pharma companies have significant opportunities to use RWE for in-market products, including to:

- Create a heat map that indicates the locations of patients who would benefit from a particular drug—such as those who are at high risk of disease progression, have a rare disease, or for whom the current care is suboptimal
- Enable predictive diagnostic tools that support practitioners' decisions
- Prioritize the actions of their medical teams in support of providers by using local, geographically adapted patient characteristics

Support Pharmacovigilance and Label Extension

After product launch, pharma companies can use RWE in a variety of ways, including to:

- Respond to a regulator's questions about drug safety or conduct postmarketing studies requested by a regulator within the required time frame
- Extend labels, such as to encompass new indications or new medical guidelines—in December 2018, the FDA launched a program to more systematically evaluate the use of RWE in changes to labeling, such as adding or modifying an indication, changing the dose or dose regimen, including a new population, or providing information on comparative effectiveness or safety

A prominent example of RWE-enabled label extension involves Pfizer's Ibrance (palbociclib). Although this breast cancer drug had undergone trials only for women, it was also proved to be effective for men on the basis of the observed positive outcomes of off-label prescriptions (using data from EHRs and postmarketing reports). In 2019, the FDA approved the drug for use in men.

How to Capture the Value

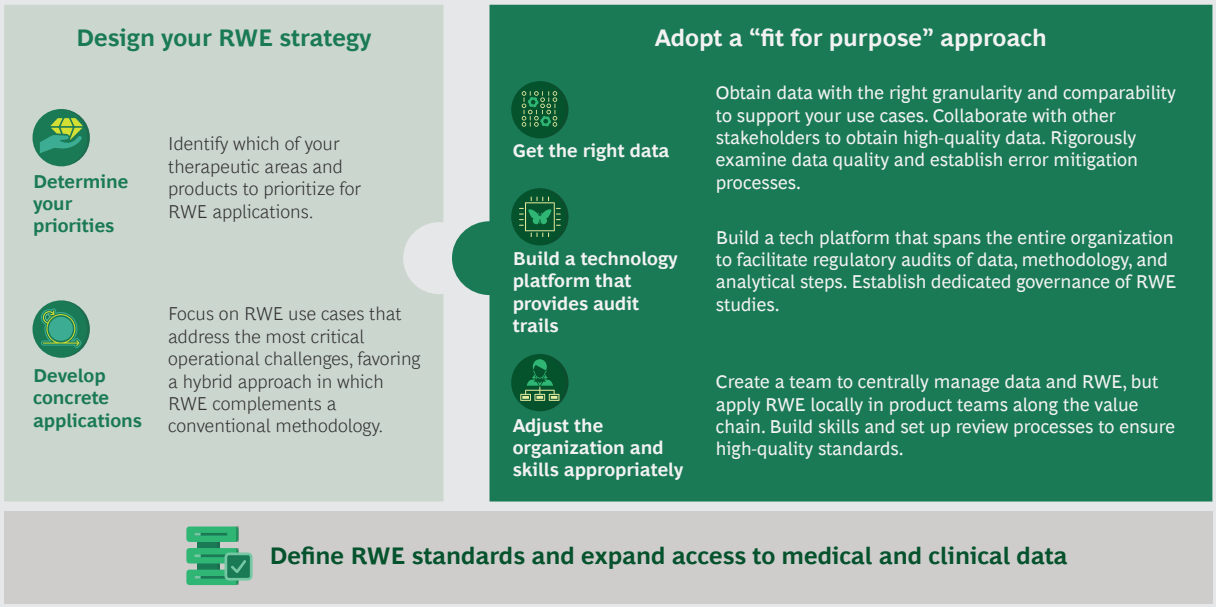
Unlocking the value from the wide variety of RWE applications entails significant challenges. As the recent COVID-19 controversies highlight, some researchers have "put the cart before horse"—diving into RWE studies before fully understanding what they needed to do in order to succeed. To lay a strong foundation for success, companies must follow the right sequence: knowing what they want and then getting what they need. In other words, they must design an RWE strategy and then adopt a fit-for-purpose implementation approach. Additionally, they should work with external stakeholders to define standards and improve data access. (See Exhibit 2.)

Design Your RWE Strategy

Before making investments in RWE capabilities, pharma companies should define a strategy.

Determine your priorities. As a first step, companies should decide which therapeutic areas and products to focus on for RWE

EXHIBIT 2 | Best Practices for Using Real-World Evidence in Pharma



Source: BCG.

applications. The prioritization should be based on a consideration of where improvements in development cycle time or label extensions would yield significant value. Companies should set priorities centrally, consolidating perspectives across the organization.

Develop concrete applications. Each business unit team should develop RWE use cases that focus on its most critical operational pain points, rather than designing abstract solutions. For instance, RWE prospective studies could be set up to complement the clinical development of high-priority candidates. The teams should include the rollout of RWE studies in their strategic objectives and annual targets.

Initially, pharma companies should favor a hybrid approach in which RWE complements a conventional methodology, instead of using RWE as a standalone practice. A hybrid approach is particularly relevant for promoting acceptance by regulators and payers and may be especially well suited to some therapeutic areas, such as rare diseases or oncology (to support drug development) and cardiology (for label extensions and postmarketing uses). Looking ahead at least two years, regulators may publish frameworks and guidelines that set out acceptable uses of a standalone RWE methodology.

ADOPT A FIT-FOR-PURPOSE APPROACH

After designing a strategy, companies must define an implementation method that is well suited to the purpose of their RWE application. To maintain quality standards and ensure the confidence of regulators and payers, a fit-for-purpose approach should cover the data, technology platform, and organization model and employee skills.

Get the right data. Embarking on RWE projects at the development stage (such as setting up a hybrid control arm) requires more-granular data than is generally available from EHRs and claims databases. To get the data they need, pharma companies could acquire more-granular data sets or collect the data themselves (such as via mobile technologies or adapted protocols). They could also collaborate with a hospital network to gain access to registries for specific diseases or drugs. In addition to ensuring that the data collected has the right granularity and comparability, an exclusive collaboration between a pharma company

and hospital network could create a competitive advantage.

For in-market studies, pharma companies can more easily acquire data sets, typically from third parties that aggregate and anonymize data from health care providers and payers. The largest commercial databases are US- and Europe-centric (such as Optum and Cegedim Health Data for EHRs and Flatiron for oncology-specific data) and typically cost several million dollars a year to license. But these databases omit significant populations, notably in China (where data needs to be licensed from local sources) and for some rare diseases (for which EHRs or claims may not be sufficient to provide the right sample size).

To access data relating to the omitted populations, pharma companies should form partnerships with academic and national stakeholders to establish dedicated registries. Collaborating with partners would also promote the acceptance of the data sets by regulators and payers because they would be less likely to suspect companies of manipulation or bias.

Using high-quality data is critical. This requires rigorously examining the quality of data sources and establishing error mitigation processes. Even when researchers use reputable data, such as from EHRs in the US, misdiagnosis and misinterpretation of results can happen routinely. Mixing data from multiple sources is particularly problematic. The *Lancet* study of hydroxychloroquine, for example, mixed good data with more questionable data, leading to a bad set of consolidated data. To avoid this pitfall, researchers should consolidate data from multiple sources only if necessary and with very great care to ensure consistency—for example, bearing in mind that doctors prescribe differently in different countries.

Build a technology platform that provides audit trails. To gain acceptance from regulators and payers, RWE studies should be easily auditable with respect to data, methodology, and analytical steps. This is often not possible today because data is typically scattered across the organization and platforms are built in silos along the value chain. The solution is for each company to develop a technology platform that spans the entire organization. By using an integrated approach and dedicated governance for RWE, a pharma company can facilitate the auditing of tools and analyses, as well ensure that it has obtained patient consent.

Adjust the organization and skills appropriately. Pharma companies have traditionally conducted RWE studies using a dedicated unit and platform, emphasizing scale—notably via bulk data acquisition. In too many cases, studies sought to reactively answer narrow questions from product teams using an overly broad set of acquired data. To effectively integrate RWE insights early in previously overlooked activities, such as clinical-protocol design, companies need to adjust their organization and employee skills.

A hub-and-spoke organization model could enable a pharma company to scale up RWE use cases while deploying resources and capabilities close to product groups. In this model, a central team is responsible for the data and methodology that local teams apply along the value chain (such as R&D and business unit teams).

Pharma companies should ensure that key employees—notably biostatisticians, clinical investigators, safety officers, and product heads—are fluent in RWE. Companies can use training and certification programs to equip employees with knowledge that allows them to apply an RWE data-driven approach in their daily work. Finally, companies should organize review processes for external studies, similar to peer reviews in scientific journals, to ensure the use of high-quality data science and ethical standards.

Define RWE Standards and Expand Access to Medical and Clinical Data

The EMA reacted to the flawed COVID-19 RWE studies by rapidly publishing guidelines that address the most glaring problems, such as underrepresentation of

at-risk cohorts. Going forward, pharma companies should collaborate with academia and health authorities to accelerate the development of broader RWE standards related to the type and quality of data, adequacy of methodologies, and expected outcomes of typical use cases. These standards should be accompanied by an auditing methodology and tools to ensure enforcement—similar to the ones already available for clinical studies.

The challenges of RWE studies during the pandemic also highlight the need for national agencies to improve access to robust and anonymized information in EHR databases. For example, in the COVID-19 study referred to earlier, the University of Oxford used the UK's National Health Service data to assess the key predictors of mortality. Because data relevant to RWE studies resides in multiple places—hospitals, payer systems, specialized clinics, and institutions—researchers need data access techniques, including anonymization, that can be deployed across the variety of databases.

The challenges encountered by RWE studies during the COVID-19 crisis point to the importance of adhering to the best practices we have outlined. They also strongly highlight the need to develop and enforce standards that will enable a more systematic approach to RWE studies. Pharma companies that take the lead in building a fit-for-purpose strategy while proactively helping to shape the regulatory environment can gain a significant competitive advantage in the coming years.

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