UNLOCKING THE PROMISE OF REAL-WORLD EVIDENCE

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The mission of *Value & Outcomes Spotlight* is to foster dialogue within the global health economics and outcomes research (HEOR) community by reviewing the impact of HEOR methodologies on health policy and healthcare delivery to ultimately improve decision making for health globally.
The promise of real-world evidence (RWE) has long been touted in the field of health economics and outcomes (HEOR) research and its principles have formed the basis of analyses and construction of models requiring robust, timely, and generalizable data. RWE continues to be leveraged to understand how well pharmaceuticals, devices, and other healthcare innovations work when implemented in practice. However, with the emergence of “big data” and increased digitization of healthcare data, RWE has created opportunities to further close the gap between clinical trials and practical clinical care. In addition to bridging this gap, RWE has begun to drive greater levels of engagement and collaboration among stakeholders, including providers, patients, payers, policy makers, and manufacturers. As Jennifer Graff, PharmD, Vice President of National Pharmaceutical Council, stated, “researchers have estimated that the use of real-world evidence could reduce trial costs between 5% to 50% to expedite safety monitoring and simplify trial and data collection,” potentially lowering overall costs for providers, payers, and—most importantly—patients. Although RWE continues to face some challenges, such as reluctance to trust its validity and reliability, a role for both RWE and randomized clinical trials (RCTs) exists in the research community. Taken together, while keeping the patients’ needs in mind, both RWE and RCTs can be utilized to better understand and manage diseases to improve outcomes for people worldwide.

The COVID-19 pandemic has made it abundantly clear that RWE is necessary for protecting and improving human health. The use of dashboards to inform our daily understanding of positive cases, positivity rates, hospitalizations, and mortality is just one example where RWE has played a critical role in understanding and managing this ongoing pandemic. Additionally, the gathering of RWE is the tenet of successful contact tracing, enabling us to understand and act quickly to manage and extinguish disease outbreaks. Practices such as social distancing, mask wearing, and hand washing have been informed mostly by data sources other than clinical trials. In short, the world needed to “get real” to tackle COVID-19 as quickly as possible in the absence of a vaccine. In the postvaccine era, undoubtedly, RWE will continue to be critical for assessing effectiveness, informing costs of vaccines (as well as safety monitoring), and guiding evidence-based policy decision making.

Recently, at the Virtual ISPOR Asia Pacific 2020 conference, Value & Outcomes Spotlight asked attendees to submit self-recorded videos describing what RWE means to them. A consistent response was that RWE should be gathered from sources wherever and whenever it happens—not only from administrative data sets and electronic health records, but also from social media, wearables, and mobile devices. The responses obtained were insightful and illustrate the importance of engaging our readers in a conversation about trends and topics in our rapidly evolving field.

We plan to produce another “Spotlight on” email series for Virtual ISPOR Europe 2020 that includes daily news stories from the conference that will appear on the Value & Outcomes Spotlight website. As always, thank you for your continued support and we welcome your feedback as we seek to reach HEOR audiences in new ways.

Zeba M. Khan, RPh, PhD and Laura T. Pizzi, PharmD, MPH
Editors-in-Chief,
Value & Outcomes Spotlight
The ISPOR Real-World Evidence (RWE) Transparency Initiative continues to make progress towards the Society’s goals in highlighting the importance of transparent research methods in secondary data-use studies, particularly for hypothesis evaluating treatment effect or comparative-effectiveness research, including safety. This month Value in Health (the official journal of ISPOR) and Pharmacoepidemiology & Drug Safety (the official journal of the International Society for Pharmacoepidemiology) have copublished the recommendations from the initiative in an article titled, Improving Transparency to Build Trust in Real-World Secondary Data Studies for Hypothesis Testing—Why, What, and How: Recommendations and a Road Map From the Real-World Evidence Transparency Initiative.1

This publication follows the position paper based on the original working group meeting in February 2019, and has been refined through the presentation of the underlying concepts at a series of ISPOR meetings. These include our conference in May 2019, the 1-day ISPOR summit in October 2019, 3 sessions presented at the ISPOR conference in Copenhagen in November 2019, plus reconvening most of the original working group members for a meeting in February 2020. It is clear that the idea of transparent research methods resonates with our stakeholders and research experts and that the urgency to continue to develop mechanisms that promote trust in the evidence-generation process and enable decision makers to evaluate the quality of methods and resulting evidence from RWE studies continues to increase.2-6

The pandemic caused by SARS-CoV-2 has put public attention on the urgent need for robust, quality, real-time clinical research that includes observational secondary data-use studies. Without previous experience in treating this virus, the healthcare system has had to resort to trial and error and shared case study experience from international sources, while also treating a tsunami of critically ill, highly infective patients. Researchers are looking to any real-time data sources to analyze trends and find patient characteristics that could predict high-risk cases. This approach has highlighted both good and bad examples of secondary data-use studies.

Never have we seen so many decision makers turning to preprints (submitted but not yet peer reviewed articles) for hints on safety signals and effectiveness of therapies (including ventilation, supportive oxygen, and steroid use), with many of these studies conducted as observational research or large simple trials conducted by hospitals treating patients in real time. While it is laudable to have these data available without proper understanding of the methods and underlying data, it is difficult to know which studies point to actionable evidence versus spurious or perhaps fraudulent results. Even in the peer review space, we have seen high-profile journals retract published observational research due to lack of transparency about the underlying data and methods,7,8 but not before high-profile studies paused enrollment partially due to information that was relevant to their patient population.9

It is clear that health economic and outcomes researchers who know the power and value of retrospective research need to continue to lead the way, shining the light on the robust methods that exist for these studies and the need for transparent study processes so that we can continue to build credibility in our research. We also need to increase our outreach, particularly to clinical journals that are used to publishing randomized clinical trial evidence, to see how we can better equip reviewers with insight and tools to understand the quality of the research before them. Clearly, there is a role for ISPOR and our members to partner more closely to educate on the merits of requiring transparent processes similar to clinical trials and perhaps even provide access to experienced scientific reviewers who could help mitigate publication of observational research that is not appropriate.

To these ends, the transparency initiative has several ongoing work streams, including efforts to build a public study registration site that is focused on hypothesis-evaluating treatment effect studies of secondary data. This initial study registration site will allow continued education of RWE researchers on good study processes, including preplanning research questions, study structure, and protocols as a prerequisite to upload. This initial site will be additive to the options currently available or
required for study registration, such as Clinicaltrials.gov and the European Post Approval Study (EU-PAS) registry. The initiative understands that many researchers with studies for regulatory intent will be required to register studies at these sites even if the variables are not optimized for secondary data-use studies. However, the RWE Transparency Initiative will be available for all other researchers, providing a simplified tailored set of questions and version control, including embargo of study and study protocols to encourage “good behavior” regarding study transparency. This includes asking researchers to attest to the amount of data-handling that has occurred with the database the proposed study will utilize prior to registering the study.

The initiative has also continued to work with multiple stakeholders to inform and evaluate our work plans, for example, aligning the first version study register variables with the structured template and reporting tool for RWE studies (STaRT-RWE). Also, we will partner with the STaRT-RWE development team under the auspices of the International Society of Pharmacoepidemiology on a joint task force that will develop a standardized protocol template specific to secondary data-use studies looking at causal inferences. This protocol working group will help inform the next generation of the Transparency Initiative’s registration site, which will continue to be optimized based on real-use cases and the protocol template, and can also feed into the regulatory sites like EU-PAS as they also look to optimize ease of use and relevance while fulfilling their government mandates.

However, tools like study registration, reporting, and protocol templates are only useful if they are used. We know from discussions with our colleagues at ClinicalTrials.gov that it was not until the International Committee of Medical Journal Editors implemented a policy that registrations of any trial are required for results to be considered for publication that site usage started to increase at a rapid rate. Incentives matter. This is another area that the Transparency Initiative will pursue as we stand up the first version of the study registration site. We need to work with our end users—journal editors, payers, and assessors—to educate them on why asking questions about study registration of submitted research is in their best interest, and encourage their active participation in providing the “carrots” (and eventually “sticks”) for adherence to these recommendations.

However, we in the ISPOR research community are very aware of what good outcomes research entails and are already holding ourselves accountable and should continue to do so publicly. By actively registering our studies, we are putting a stake in the ground and holding up health economics and outcomes research (HEOR) to the same bar as any other clinical research. HEOR deserves a seat at the evidence-based medicine table. We would even say that evidence-based medicine cannot fully occur until it includes HEOR. But to be there, we need to continually foster the validity of our research and research methods. Now is the time to highlight and increase the external perception of what we do and how we do it. We welcome your input and ask you to watch for the announcement of the ISPOR-sponsored study registry.

References


1 **Real-World Evidence: A Reality Check**
(Managed Healthcare Executive)
Proponents of real-world evidence say it will yield information that is both more targeted and more thorough than the evidence that clinical trials can provide. But that doesn't mean real-world evidence research is easy to do—or inexpensive—notwithstanding the relative cost of the randomized trial. What's more, electronic health records and insurance claims may contain a wealth of information, but neither are designed for medical research. And if wearable devices were to live up to merely half of their hype, even more data would come pouring into the mix. Collecting, organizing, and understanding data requires skill, time, and money and many current computer systems just aren't up to dealing with that data firehose.
Read more.

2 **MHRA Posts Suite of Post-Transition Guidances**
(Regulatory Focus)
The UK’s Medicines and Healthcare products Regulatory Agency (MHRA) in September released more than 2 dozen guidance documents explaining how drugs, medical devices, clinical trials, and more will be regulated after the Brexit transition period expires on January 1. Read more.

3 **For the First Time, Drug Makers and PBMs Must Jointly Face an Insulin Price Fixing Lawsuit**
(Pharmalot)
A federal judge ruled that Harris County, TX, USA, can proceed with a lawsuit accusing several drug makers and pharmacy benefit managers of conspiring to fix prices for insulin. This marks the first time that these companies will have to collectively defend their role in the rising cost of the life-saving diabetes medicine. In a lawsuit filed last year, Harris County officials claimed taxpayers were “fraudulently overcharged” for ongoing and drastic price hikes for a medication that has not substantively changed in many years. From 2013 to 2018, the county maintained it paid $27.5 million for insulin due to an allegedly misleading pricing scheme involving both drug companies and the biggest pharmacy benefit managers. Read more.

4 **EMA Consults on Using Registry Studies as Real-World Evidence Source**
(Pink Sheet)
A draft EU guideline explains how disease registries can be used to supplement evidence in the pre-authorization phase and provide infrastructure for post-authorization evidence generation. Read more.

5 **Democrats Slam Teva, Celgene Execs for Large Price Hikes**
(Fierce Healthcare)
House Democrats tore into several pharmaceutical executives for continuing to raise prices for certain drugs even as they allocated limited funding to research and development. The House Committee on Oversight and Government Reform held the first in a 2-day hearing September 30, 2020 on unsustainable drug prices. The hearing follows a report released by the committee that found drug maker Celgene, now part of Bristol Myers Squibb, raised prices for cancer drug Revlimid multiples times over the years to meet sales targets, and that Teva Pharmaceuticals raised prices for multiple sclerosis drug Copaxone despite low research and development costs. Read more.

6 **Drugs Aren’t the Reason the United States Spends So Much on Healthcare**
(Kaiser Family Foundation)
Voters care a lot about drug prices, but they’re not the main reason the United States spends so much on healthcare. The United States spends twice as much per person as other wealthy nations, according to a new Peterson-Kaiser Tracker analysis, and hospitals and outpatient care are the primary culprits. Read more.

7 **CMS Releases its Annual IPPS Final Rule: Key Updates for Manufacturers**
(PRMA Consulting)
On September 2, 2020, the Centers for Medicare & Medicaid Services (CMS) released its annual Inpatient Prospective Payment System (IPPS) final rule, which applies to hospital discharges occurring on or after October 1, 2020 and will impact approximately 3200 acute care hospitals across the United States. While the ruling is made up of enormous detail across a 2160-page document, there are several key updates that will have implications on manufacturers in months and years to come. Read more.

8 **ICER to Assess Treatment for Alzheimer’s Disease**
(ICER)
The Institute for Clinical and Economic Review (ICER) announced September 29, 2020 that it will assess the comparative clinical effectiveness and value of aducanumab (Biogen) for treatment of Alzheimer disease. An FDA decision on aducanumab is expected in early 2021. The assessment will be publicly discussed during a meeting of the California Technology Assessment Forum in May 2021, where the independent evidence review panel will deliberate and vote on evidence presented in ICER’s report. Read more.
Pseudo-Understanding: An Analysis of the Dilution of Value in Healthcare (BMJ Quality & Safety)
Management concepts cycle through healthcare in trends lasting 3-5 years. This may hinder policymakers, healthcare managers, researchers, and clinicians from grasping the intricacies of a management concept and prevent organizations from realizing the potential of these concepts. Researchers sought to characterize how the newest management concept, value-based healthcare, is used and understood in the scientific literature. Read more.

Utilizing Patient and Public Involvement in Stated Preference Research in Health: Learning From the Existing Literature and a Case Study (The Patient–Patient-Centered Outcomes Research)
Publications reporting discrete choice experiments of healthcare interventions rarely discuss whether patient and public involvement activities have been conducted. This paper presents examples from the existing literature and a detailed case study from the National Institute for Health Research-funded PATHWAY program that comprehensively included patient and public involvement activities at multiple stages of preference research. The paper describes different stages at which it is possible to effectively incorporate patient and public involvement across preference research, including the design, recruitment, and dissemination of projects. Read more.

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RESEARCH ROUNDUP

Section Editor: George Papadopoulos, BSc(Hons). GradDipEpi, MAICD Partner & Director, Lucid Health Consulting & School of Medicine, UNSW, Sydney, NSW, Australia

The articles featured in this issue’s Research Roundup look at the current state of real-world evidence (RWE). Real-world data (RWD) and RWE are playing an increasing role in healthcare decisions. The healthcare community is using these data to support coverage decisions and to develop guidelines and decision support tools for use in clinical practice, while developers of pharmaceuticals are using RWD and RWE to support clinical trial designs and observational studies to generate innovative and new treatments. We have identified 5 research papers that encapsulate these characteristics and are worth reading.

Role of Real-World Evidence for Oncology Product Registration in the United States: A Review of Approvals by the US Food and Drug Administration from 2015 to 2019

Summary
There are few concrete examples of RWE used to support clinical development in regulatory filings despite growing interest in this field. This study systematically reviewed the US Food and Drug Administration’s (FDA) oncology approvals from 2015-2019 to identify cases of use of RWE that led to FDA decisions. Ninety-three approved new drug applications and biologics license applications were identified. Only 6 (6.5%) included RWE in support of efficacy, approved on or after 2017, and these data were largely retrospective studies that contextualized results to pivotal trials, with primary endpoints including overall survival, overall response rate, and time-to-treatment discontinuation. Among cases with RWE, all study designs were retrospective and 3 were database analyses, and 1 each of expanded access program, meta-analysis, and chart review analyses.

Relevance
In the past 5 years, only a few FDA decisions incorporated RWE in oncology drug approvals but when utilized, RWE has been a complement rather than a supplement for clinical trial data. The key determinants for successful use of RWE in FDA decision making are early engagement, a priori protocol development, and robust research design.

Feasibility of Using Real-World Data to Replicate Clinical Trial Evidence

Summary
This was a cross-sectional study of US-based clinical trials published in 2017 in the top 7 highest impact general medical journals that looked to establish how they could be feasibly replicated using observational data from insurance claims and/or electronic health records. Of the 220 trials analyzed, 33 (15.0%) could be replicated using observational data because their intervention, indication, inclusion, and exclusion criteria, and primary endpoints could be routinely ascertained from insurance claims and/or electronic health record data.

Relevance
The research findings suggest the potential for observational data to complement but not completely replace clinical trials and that, although the increasing use of RWE in medical research presents opportunities to complement, supplement, or even replace some clinical trials, observational methods are not likely to obviate the need for traditional clinical trials any time soon.

Economic Evaluations Informed Exclusively by Real World Data: A Systematic Review

Summary
A very timely and thorough systematic review via the established databases regarding the quality of full economic evaluations developed using RWD. The authors used the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist to assess the methodological quality of the studies. Their initial search identified a massive 14,011 studies, of which only 93 were included for review of their methodological quality, after an initial 593 were potentially eligible following review of title and abstract. Article selection and reasons for exclusion, mainly those studies using economic evaluation models, studies not using RWD, or those that did not perform complete economic evaluations. The most frequently assessed illnesses were neoplasms while the most evaluated interventions were pharmacological. The main source of costs and effects of RWD were information systems and the most frequent clinical outcome was survival. However, only 47% of studies met at least 80% of CHEERS criteria.

Relevance
This review highlights that the use of RWD in carrying out economic evaluations with individual patient data is an increasingly common practice; however, more attention should be paid to the reporting of methodologies and results in economic evaluations. Use of the CHEERS checklist showed that there are important aspects of RWD that are not considered and that it would be valuable to have available an economic evaluation checklist that includes RWD.
Developing a Framework to Incorporate Real-World Evidence in Cancer Drug Funding Decisions: The Canadian Real-World Evidence for Value of Cancer Drugs (CanREValue) Collaboration

Summary
While the potential value of RWE is well established in oncology research, technical and methodological challenges exist in its generation and use by different stakeholders. The authors propose a framework; the CanREValue collaboration (Canadian Real-world Evidence for Value of Cancer Drugs) aims to address these challenges and establish a framework for Canadian provinces regarding the generation and use of RWE for cancer drug funding decision making. The CanREValue collaboration will focus on the generation of RWE using RWD collected from existing population-level administrative health databases. The CanREValue collaboration has established 5 formal working groups to focus on specific processes in the generation and use of RWE for cancer drug funding decisions in Canada; 1) Planning and Drug Selection; 2) Methods; 3) Data; 4) Reassessment and Uptake; 5) Engagement.

Relevance
The framework can potentially enable the reassessment of cancer drugs, refinement of funding recommendations, and use of novel funding mechanisms by decision makers/payers across Canada to ensure the healthcare system is providing clinical benefits and value for money. It will be of value to follow this collaboration over its 4-year lifespan as the working groups act collaboratively to develop a working and validated framework and evaluate how it will help integrate the final RWE framework into the Canadian healthcare system.

Real-World Evidence Use in Assessments of Cancer Drugs by NICE

Summary
The authors reviewed the single technology appraisals (STAs) of cancer drugs conducted by the National Institute for Health and Care Excellence (NICE) to establish how RWE has been used. The STAs published by NICE from April 2011 to October 2018 that evaluated cancer treatments were reviewed. One hundred and 13 relevant STAs were identified and analyzed, of which 96% included some form of RWE within the company-submitted cost-effectiveness analysis. The most common categories of RWE use concerned the health-related quality of life of patients (71%), costs (46%), and medical resource utilization (40%). Interestingly, while the sources of RWE were routinely criticized as part of the appraisal process, the authors identified only 2 cases where the use of RWE was overtly rejected, concluding that in the majority of cases, RWE was accepted in cancer drug submissions to NICE. The key criticisms of RWE in submissions to NICE were typically concerned with specific data sources or analytical methods and the applicability of these to the decision problem.

Relevance
The use of RWE in NICE submissions of cancer drugs was found to be extensive, and in general appeared to have provided a valuable source of information to aid the decision making. The recommendation is that submissions to NICE should aim to proactively acknowledge the common criticisms leveled at inclusion of RWE through clear justification of the approaches taken to analyse RWE and the relevance of the RWD source.
Real-World Effectiveness in Oncology: Plotting a Path Forward

Section Editors: Soraya Azmi, MBBS, MPH, Beigene, USA; Agnes Benedict, MSc, MA, Evidera, Budapest, Hungary

Predicting Real-World Effectiveness of Cancer Therapies Using Overall Survival and Progression-Free Survival From Clinical Trials: Empirical Evidence for the ASCO Value Framework

Darius N. Lakdawalla, Jason Shafrin, Ningqi Hou, et al.


One particularly appealing hope that many have had for real-world evidence is its potential ability to reduce our reliance on clinical trials in assessing new and innovative treatments. This optimism pinned on real-world data and evidence is true across all diseases and indications, yet there is much work to be done to achieve this end. The paper by Lakdawalla et al assists us in understanding the path forward, particularly in the field of oncology.

Clinical trials, the gold standard for assessing safety and efficacy, are designed around endpoints or outcomes that are known for that disease or indication. In oncology, these are overall survival, progression-free survival, or time to progression. Despite our reliance on trials, it is well recognized that trials are a unique and highly selective environment, leaving a need to understand how the drug will perform among an unselected, or at least, less selected group of patients that physicians face in their day-to-day practice. Real-world evidence is attractive for this reason. The second higher goal that we may wonder about is whether real-world evidence endpoints can match up to gold standard clinical trial endpoints, and if they do, how reliably so. This is the work that was done by the authors.

The authors examined the relationship between randomized clinical trials, measured efficacy (overall survival, progression-free survival, and time to progression) against real-world overall survival. Real-world overall survival as reflected by real-world mortality hazard ratios was measured against randomized clinical trial overall survival or clinical trial survival surrogate endpoints. Surrogate endpoints considered were progression-free survival or time to progression. In their methodology, the authors described selecting clinical trials in identified cancer indications of interest (breast, colorectal, lung, ovarian, and pancreatic cancers) that reported overall survival, progression-free survival, and time-to-progression endpoints that could be compared against survival of patients in the real world using the SEER-Medicare database.

Trials selected had to have regimens with phase III pivotal trials reporting both overall survival and progression-free survival or time to progression, and regimens had to be approved by the FDA before 2009 so that patients in the real world had at least 2 years of survival data captured in the SEER-Medicare database. Through their selection process, 29 pivotal trials met the study’s inclusion criteria. Next, the authors selected patients from the SEER-Medicare database that met inclusion and exclusion criteria of each of the clinical trials according to the relevant diagnosis and real-world treatment regimen that matched the corresponding clinical trial regimens. Other inclusion criteria were also applied (eg, patients were required to have initiated cancer treatment within 90 days of diagnosis, patients could appear in the sample multiple times if they received more than 1 of the treatments of interest, and patients were assigned to treatment of comparator arm depending on their tumor and therapy received).

The comparison between real-world endpoints and trial endpoints was carried out by assessing whether treatment efficacy derived from randomized clinical trials was able to predict the real-world overall survival. Cox proportional hazards regression analysis was used, with separate analyses performed to predict real-world overall survival using trial overall survival or trial surrogate endpoints. Sensitivity analysis was also performed to test the robustness of results. For example, in the main model, patients in the baseline cohort were limited to those who met the randomized clinical trials inclusion and exclusion criteria. The authors also examined a “full cohort” that were all patients receiving the relevant treatment in the SEER-Medicare database.

The results of the study found that after applying inclusion/exclusion criteria, there were 18,148 unique patients across 21 different randomized clinical trials divided among the 5 cancer indications of interest (8 trials were excluded because there were 10 or fewer patient observations). For example, in lung cancer, 12,146 patients met clinical trial inclusion/exclusion criteria. Their results showed that the real-world mortality hazard ratios were not different from those of randomized clinical trials, with the percentage difference being 0.6%, 95% CI -3.4-4.8%. On the other hand, the real-world mortality hazard ratios were significantly different from the randomized clinical trials surrogate endpoint surrogate hazard ratio (SHR) at about 16%, 95% CI 11%-20.5% (ie, significantly lower than what would be predicted by the randomized clinical trials). They further looked at how their assumptions compared against the ASCO value framework and found that there “was a large difference in only 4 out of 21 studies. In the others, the difference was either small or not statistically significant.”

This study showed that real-world overall survival endpoints can be usefully compared against clinical trial overall survival endpoints, but perhaps with surrogate endpoints there needs to be a “discount” factor built in. The paper could be a worthwhile read for anyone who is interested in how real-world evidence can be used to understand the nature of its own relationship to, and against, the gold standard of clinical trial endpoints. Although the application in this study was in oncology, the same conceptual framework could be applied to any other disease area.
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UNLOCKING THE PROMISE OF REAL-WORLD EVIDENCE

BY MICHELE CLEARY
RESEARCHERS TODAY ARE FACED WITH AN EVER-GROWING wealth of real-world data. While long used for safety surveillance, recent mandates in the 21st Century Cures Act and Prescription Drug User Fee Act are accelerating the use of real-world evidence in regulatory decisions, including secondary indications for already approved drugs. Today, real-world-evidence-based insights are driving not only regulatory decisions, but also reimbursement decisions.

This year, the COVID-19 pandemic has further fueled real-world evidence analyses. Yet, whether these real-world-evidence-based decisions are reliable or accurately remains unclear. William H. Crown, PhD; Lucinda Orsini, DPM, MPH; Nirosha Mahendraratnam Lederer, PhD; Shirley Wang, PhD; and Diana Brixner, RPh, PhD shared their thoughts on the use of real-world evidence for both regulatory and assessment purposes, and discussed current challenges, future opportunities, and whether real-world evidence is truly achieving its goal—helping to ensure greater patient access to more effective treatments.

Limits of Randomized Clinical Trials

William H. Crown, PhD, Distinguished Research Scientist at The Heller School for Social Policy and Management at Brandeis University in Waltham, Massachusetts, USA, began the discussion by revisiting some intrinsic limitations of randomized clinical trials. “The fact that something is randomized doesn’t necessarily give you the right answer if it isn’t a large enough trial and well designed.” For Crown, real-world evidence can augment and facilitate randomized clinical trials. “I think there are many cases where we’re doing randomized clinical trials now, when we could actually conduct quasi-experimental design-type studies with real-world data and achieve the same thing much more quickly and at lower cost.”

“Because drugs are frequently prescribed off-label, the data often exist in claims databases and electronic medical record data,” said Crown. “Companies can basically simulate the trial and these sorts of quasi-experimental design studies can generate very similar estimates to the randomized trials,” he explained. He highlighted cardiovascular disorders and diabetes as conditions where real-world evidence looks particularly promising.

Expanding Regulatory Support for Real-World Evidence

Incentivized by market changes and legislation like the 21st Century Cures Act, pharmaceutical companies are expanding their use of real-world evidence to test secondary indications for already approved drugs and to conduct ongoing safety surveillance.

Crown also emphasized the value of real-world evidence in single-arm trials, particularly in rare conditions when insufficient numbers of patients impede randomization to a comparator group. “There’s a lot of interest in so-called ‘external comparative trials’ using data drawn from databases to find a comparison group of persons similar to those being treated in one-arm trials.”

Insight Into Underrepresented Groups

Crown also heralded these real-world evidence trials as an important tool for examining treatment effects in diverse patient populations (ie, groups often underrepresented in clinical trials). Regulatory trials often focus on narrowly defined subgroups to amplify the precision of estimated treatment effects. But narrow inclusion and exclusion criteria limit generalizability. “In actual practice, these drugs are used in broader patient populations,” said Crown.

He emphasized the importance of target trials, which, by running the trial within a real-world database, allow for the analysis of treatment outcomes within specified subgroups. Not only can these trials be conducted quickly, they can examine treatment effects across different sociodemographic groups (ie, by race, ethnicity, gender, and geography), bringing critical insight into our understanding of treatment effects in these often underrepresented groups.

Growing Acceptance by Regulators and Assessment Bodies

Lucinda Orsini, DPM, MPH, Associate Chief Science Officer at ISPOR in Lawrenceville, NJ, USA, reflected on the increasing acceptance of real-world evidence by both regulatory and assessment bodies. “I think regulators are always on the tip of the spear. They are the first ones to see that, with a rare disease or an area where there are very few treatments, companies are trying to bring these options forward as quickly as they can.”

Such cases, Orsini noted, have driven regulators to adopt a more flexible stance on real-world evidence. “Regulators are starting to see that more data are better than less data, even if the data aren’t what they would call ‘perfect, clinical trial, phase III data.’”

COVID-19 Spurring Real-World Evidence Acceptance

But under the COVID-19 pandemic, Orsini sees many assessment bodies becoming more receptive to real-world evidence. She used the United States as an example, where many legislative bodies are mandating payers to cover COVID-19-related diagnostic testing, treatments, and healthcare services. In these cases, effectiveness information is limited, leaving payers to ask whether they can conduct assessments given the lack of clinical information.

Orsini sees an opportunity for the industry and payers to work together to enact more reasonable usage agreements when faced with such limited product information. “I think COVID-19 brought outcomes-based contracting even more to the fore,” Orsini said. “Payments have their own data to conduct their own data analyses of treatment outcomes within their own patients. “However, the manufacturers are going to want to look under the hood and see how that’s calculated,” she added.

“My mantra is you have to use the right data to answer the right question. If you don’t understand what the data are telling you, you could get some misinformation and potentially some harmful decision making, as is being seen now with COVID-19.”
Need for Greater Transparency
To ensure effective partnerships, Orsini stressed the need for greater transparency. “Everyone must understand where that data can be useful and where it’s not so useful. I think that’s the kind of transparency we need.” She added, “Unless we understand how data sets are pulled and put together, we just don’t really know what we’re getting into and why.”

But while transparency of methods and analysis is critical, she warned we must also understand how the data were collected and where they came from.

“Transparency can lead to more of an informed interpretation about what these data really can and can’t do.” Orsini said, “It’s a continuum, and you have to put the data into context in the question that you have at hand to see how it might be able to help you. It’s probably not the panacea, but it can’t be completely discounted either.”

To address this need for transparency, Orsini proposed opening dialogue with end users of the data, letting users “follow the breadcrumbs all the way through your process, to the results, and then figuring out better ways to communicate about the study design and what the results could mean."

Multifaceted Nature of Transparency
Nirosha Mahendraratnam Lederer, PhD, Managing Associate at the Duke-Margolis Center for Health Policy, Durham, NC, USA, echoed this call for greater transparency. “I think transparency is key. The more up-front you are with what you plan on doing with the data, the more it builds trust in the studies.”

To aid transparency, she proposes routine prespecification and registration of real-world evidence study protocols. However, she clarified that these study protocols support transparency of the analysis, noting that “data curation transparency is something quite different.”

A Call for Data Curation Transparency
Lederer noted that while many researchers may already employ high-quality curation practices, problems remain from an evaluation standpoint because of poor documentation as well as a lack of universal standards for data curation and measures of fitness. These need to become not only more transparent, but accessible.

To address this, her group proposes guiding checklists. “We are aiming for the development of a minimum standard list of fitness-for-use checks, focusing first on reliability. We should be concerned that people might keep cutting data in different ways to possibly get an answer they want,” she warned. “I think as a best practice, you should prespecify and justify what curation practices you plan on using. That being said, we often learn lessons along the way that may require changing our original plan. That’s okay, but it should be documented, and again, justified.”

Lessons From COVID-19
Lederer also discussed how COVID-19 has accelerated decision makers’ use and understanding of real-world evidence. “In the context of COVID-19, we’ve had to rely on real-world data and real-world evidence because that’s all we had.” However, she warned that the demand for real-world evidence could lead researchers into “challenging situations when they try to force a data set or when data aren’t reliable.”

“My mantra is you have to use the right data to answer the right question. If you don’t understand what the data are telling you, you could get some misinformation and potentially some harmful decision making.” However, she remains optimistic as there is unprecedented collaboration in the real-world evidence community to fight COVID-19. There is so much sharing not only of lessons, but also even code to improve both data quality and analysis methods to generate better real-world evidence.

Improving the Real-World Evidence Ecosystem
In response to the expanded use of real-world evidence, Lederer and her colleagues identified significant lessons learned from the current COVID-19 pandemic. “We’re really thinking about how you advance the real-world data ecosystem. We’re looking too at incentives to improve data collection at the point of entry (eg, electronic medical records), while improving curation at the back end.” This, she feels, could improve data efficiency and alignment.

Lederer also emphasized the need for the right evaluators and reviewers for these studies, suggesting evaluation criteria to guide reviews. “The role of real-world evidence is different for new products versus products already on the market (eg, repurposed therapies). And we want to make sure that people with the right skillset are evaluating that research.

“The really that pays are interested in all of the kinds of measures that you have in real-world data—the actual cost and avoided healthcare utilization, hospitalizations, longer-term outcomes—outcomes that you typically have difficulty measuring in trial.”

“We’re also thinking about novel data sources. How can we use patient-generated health data to complement our traditional real-world data sources? What are lessons learned related to outcomes and end points with remote patient monitoring?” Lederer closed by saying, “Even though we’re learning about digital tools in the clinical trial setting through decentralized trials, digital tools are frequently used in the real-world setting. And if we are learning how digital tools are capturing outcomes of interest in the trial setting, that might open up the use of these tools and validation of these tools in the real-world setting.”

The Value of Replication
Shirley Wang, PhD, Assistant Professor of Medicine at Harvard Medical School, Cambridge, MA, USA, spoke of the value of replication. “I think one of the strengths of real-world evidence is that increasingly these data sources are accessible to multiple investigators who can verify replicability and the robustness of the decisions, as opposed to primary data collection, which is a lot harder to replicate.”
Wang is part of the team leading the REPEAT Initiative, a large-scale replication project based within the Division of Pharmacoepidemiology and Pharmacoeconomics at Harvard University. REPEAT aims to independently replicate a random sample of 150 peer-reviewed real-world evidence studies. This project is part of a wider movement across many scientific disciplines (eg, psychology, economics, bench sciences) to replicate prior research findings.

Wang shared that this movement has fueled a “replication crisis,” driving researchers to examine what can be changed within their research culture to improve the reproducibility of research findings. She emphasized that her team was measuring replicability, not study validity. “They’re different, but related. Replicability can make it easier for you to assess validity because you understand what was done, but it does not equal validity.” She continued, “We want validity and replicability helps us get there.”

Strong Correlations Found
Using the prior work of the ISPOR/ISPE joint taskforce, Wang and her colleagues established a checklist of specific parameters they deemed necessary to facilitate reproducibility and assess validity. For a subset of 150 studies, Wang and her colleagues licensed access to the same databases, using the same years of data, and the same methodologies. And Wang emphasized that study results had been redacted, so her team could attempt replication without knowing the actual results.

As reported by Wang, the team found a strong correlation between the original effect size and the replication effect size (correlation coefficient = 0.8). “If you look at the relative magnitude of the original effect size compared to the replication effect size, the relative magnitude is the median that we use to indicate that we’ve hit it spot on.” However, she noted that there is a substantial subset of studies for which the team was not able to replicate its findings, despite using the same source data and the same methods.

Need for Better Documentation
Wang did highlight some documentation challenges to their study replication project, namely, how choices are made to generate the evidence. “We need all of that information in order to truly understand, do we agree with the choices that you’re making, does it raise any validity concerns? What are the choices that are being made in order to generate the evidence?” To aid in communication, Wang recommends adding design diagrams as a high-level summary of temporal windows in the design of a study.

Payer Perspectives of Real-World Evidence
Finally, Diana Brixner, PhD, RPh, Professor in the Department of Pharmacotherapy at the University of Utah College of Pharmacy, Salt Lake City, Utah, USA, conveyed thoughts from the payer perspective. In her view, the importance of real-world evidence research to payers has grown with its use in reimbursement decisions. “It’s really that payers are interested in all of the kinds of measures that you have in real-world
data—the actual cost and avoided healthcare utilization, hospitalizations, longer-term outcomes—outcomes that you typically have difficulty measuring in trial.”

Brixner emphasized that payers also want to see trial research validated against real-world evidence, given that increasingly expensive drugs are coming to market with less and less data—a significant issue with oncology, gene therapy, and other specialty drugs. Because the FDA has accelerated patient access to these drugs by lowering barriers to market entry, fewer clinical data exist to make reimbursement decisions upon launch.

“Transparency can lead to more of an informed interpretation about what these data really can and can’t do.”

To Brixner, real-world evidence could help resolve this issue. “I think real-world studies need to be taking place in order to validate clinical trial results and to support reimbursement decisions.

“The expectation has been that that industry is coming out and describing their potential new product: where they think the target population would be, what the benefit would be, what the potential price might be.” But Brixner noted that while health plans may be willing to reimburse for a given indication initially, future reimbursement would ideally hinge on real-world evidence studies within the health plan’s population. “Validate what you said it was going to do for our populations based on your clinical trials.”

But according to Brixner, payers are having difficulty “holding the line” of hinging future reimbursement on real-world evidence. “There’s a real struggle getting access to validated studies in a timely manner for reimbursement decisions,” she said. Health plans are facing staffing and data-quality challenges to adequately validate prelaunch claims, while manufacturers see no real incentives to support real-world evidence studies.

Will payers actually discontinue reimbursement due to insufficient real-world evidence? In Brixner’s view, industry feels that avoiding these real-world evidence studies may be a gamble worth taking, given that payers are unlikely to no longer cover their products. “That is the sort of balance we exist in right now. How do we move from this point?”

Brixner suggested a possible solution in value-based pricing. “In the United States in particular, a lot of the pricing is driven by these rebate schemes.” She continued, “I think the model needs to change. And I think that the model needs to start being this value-based contracting driven by performance-based research agreements, where payers, researchers, and manufacturers collaborate together in everyone’s best interest. And right now, that’s not happening.”

About the Author
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By the Numbers: The Current State of Real-World Evidence

Section Editor: The ISPOR Student Network

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On 17 June 2020, the first COVID-19 health preference research roundtable was held as an open meeting of the minds, allowing a healthy exchange of ideas between study teams and other attendees interested in the area.

Like the rest of the world, the pandemic has reshaped the lives and livelihoods of scientists in the health economics and outcomes research community. Many investigators in health preference research reacted by conducting empirical studies to better understand the value of health and health-related alternatives affected by COVID-19. The group identified 18 health preference studies currently under review or ongoing. On 17 June 2020, the first COVID-19 health preference research roundtable was held as an open meeting of the minds, allowing a healthy exchange of ideas between these study teams and other attendees interested in the area. From that discussion, this summary characterizes the state of science for the broader scientific community and for regulators and other decision makers looking for preference evidence regarding COVID-19. As defined by the International Academy of Health Preference Research, a health preference study uses observational and experimental methods to collect empirical evidence on health-related choices. The 18 studies discussed here focused on stated preferences, specifically testing the causal relationships between attributes and preferential choice behaviors related to COVID-19. Due to their preliminary nature, the studies are not cited directly here; instead, this summary will attempt to describe initial experiences of the health preference research community, not the findings of individual studies.

Given that COVID-19 is a new topic in health preference research, it was remarkable to hear about so many independent studies from Australia, Canada, China, France, Germany, New Zealand, The Netherlands, the United Kingdom, and the United States. Most sought to study preferences of the general population on alternative policies and the tradeoffs involved, either in a single country or in multiple countries. Others focused on individual health interventions, attempting to predict uptake of COVID-19 vaccines and of contact-tracing apps. Many topics remain untouched, such as clinical trial participation, labor decisions, testing, and long-term care. COVID-19 has affected nearly all aspects of our daily lives and COVID-19 health preference research will likely expand immensely over the coming months with little risk of duplication. This article emphasizes the lessons learned that are particularly relevant when conducting a COVID-19 health preference research study.

**COVID-19 Health Preference Research: 4 Lessons Learned**

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study objectives with dissemination plans to avoid the potential obsolescence of preference evidence due to changes in the context or as respondents gain greater firsthand experience with COVID-19.

**Second Lesson Learned**
The second lesson is that nearly all epidemiologic interventions and their social impacts are legitimately complex, which makes them challenging to convey to the general population in a health preference study. Furthermore, trading off among attributes often presents a moral dilemma, calling for the interpretation of a philosopher as much as an economist. For example, choosing to wait for a more effective vaccine may imply time preferences, but also has distributional consequences within the population. In most countries, the burden of COVID-19 in terms of health and employment has been far from uniform.

**Capturing preference evidence now on tradeoffs and priorities can provide an evidentiary basis for health system reforms in the near- and long-term. Some researchers are using this moment to develop innovative prioritization tools (eg, ventilator allocation) that may have applications across multiple future areas.**

**Third Lesson Learned**
The third lesson concerns the inelastic demand for goods and services, such as masks, contact tracing apps, and vaccines. Some people are nontraders who are implacably in favor of or against a good or service (eg, anti-vaxxers), regardless of the attributes. Such persons absolutely will or will not comply with public health recommendations. Knowing the proportion of nontraders is required to accurately predict uptake; however, surveying their preferences on alternatives is uninformative. Some researchers have argued that stated preference surveys are bad at predicting uptake but good at quantifying rates of substitution. The ideal approach may be to pool stated and revealed preference evidence to identify both rates of substitution and predicted uptake. In any case, it is important to acknowledge the limits of preference evidence when capturing the factors that drive real-world behaviors (eg, working to support a household).

**Fourth and Final Lesson**
The last lesson is to recognize that the world is in the midst of a pandemic like no other in terms of infectious spread and media attention. Understanding what drives uptake and other health-related behaviors is critically important for nearly every country. Capturing preference evidence now on tradeoffs and priorities can provide an evidentiary basis for health system reforms in the near and long-term. Some researchers are using this moment to develop innovative prioritization tools (eg, ventilator allocation) that may have applications across multiple future areas. Even when this challenge is overcome, there will likely be another “someday” with similar traits.

The attendees of the first roundtable expressed unanimous support for COVID-19 health preference research and hoped to see these and many more studies published in the coming months to inform regulatory decisions, economic evaluations, clinical practice, and health policy.
Beyond Harmonization: Implementing Standardized Outcome Measures to Support Value-Based Care

Michelle Leavy, MPH, OM1, Inc, Boston, MA, USA; Elise Berliner, PhD, Agency for Healthcare Research and Quality, Rockville, MD, USA; Rich Gliklich, MD, OM1, Inc, Boston, MA, USA

As our health system increasingly moves toward data-driven approaches to value-based care and quality improvement, standardization of outcome measures will be essential to support efficient capture of meaningful data and to enable comparisons of outcome measures across providers and across treatment and diagnostic options.

Value-based care has received significant attention in recent years as an approach to improving patient outcomes while controlling healthcare costs. Value-based initiatives often rely on comparisons across providers or across diagnostic and treatment interventions to identify best practices and areas for improvement in quality, safety, and efficiency. These comparisons are built on measures that examine the quality of care provided and the resulting patient outcomes.

Many types of measures are used in value-based programs and quality improvement initiatives. Process-of-care measures examine whether a specific action was taken by the healthcare provider and have a long history of use in quality improvement efforts. More recently, attention has shifted to outcome measures, meaning measures that look at patient outcomes. For example, in depression, screening (ie, was the patient screened for depression?) is a process-of-care measure, while the patient’s achievement of remission at 6 months is an outcome measure.

Measure selection, definition, and implementation is critical for the success of value-based care initiatives. Measures must be meaningful to clinicians and patients, defined clearly so they can be captured consistently across practices and care settings, and feasible to implement within routine clinical practice. Yet, in many clinical areas, there is a lack of agreement on which outcomes to measure and how to define those measures. For example, in asthma, several different definitions of an asthma exacerbation are used in research studies, quality improvement efforts, and clinical practice. In lumbar spondylolisthesis, while there is broad agreement on the importance of measuring physical functioning, there is less agreement on the specific domains of interest, and a variety of instruments are used in different studies.

This wide variation in the outcomes that are measured in research studies, quality improvement efforts, value-based care initiatives, and clinical practice makes it challenging, if not impossible, to compare findings and connect data across data sources. At the provider level, data may need to be documented multiple ways to meet the needs of different programs, introducing unnecessary data entry burden. At the research level, it may be infeasible to combine or link existing datasets to address new research questions, and systematic reviewers may be unable to aggregate and compare results from different studies. At the level of learning health systems and value-based care initiatives, it becomes increasingly difficult to connect data from research to clinical practice to patient outcomes to identify best practices and target specific areas for improvement.

Standardized Outcomes as a Path to Value-Based Care

Standardizing outcome measures is an essential first step to reduce this unnecessary variation and build data infrastructure to support research, clinical practice, quality improvement, and value-based care. To facilitate standardization, the US Department of Health & Human Services, led by the Agency for Healthcare Research and Quality (AHRQ) and in collaboration with the US Food & Drug Administration and the National Library of Medicine, has supported the development of the Outcome Measures Framework, a conceptual model for classifying outcome measures across a range of clinical areas. This framework can be used to guide the selection and definition of new outcome measures and to harmonize existing outcome measures.

AHRQ recently supported an effort to use the Outcome Measures Framework to develop minimum sets of standardized outcome measures in 5 clinical areas—atrial fibrillation, asthma, depression, non-small cell lung cancer, and lumbar...
The standardized outcome measures are intended as core sets of outcomes that can be captured in routine clinical practice and in research settings; supplemental measures may be added to address specific purposes. By standardizing measures across patient registries and other data collection efforts, AHRQ hopes to spur the development of data infrastructure to support patient-centered outcomes research and learning health systems. Registries operate within each component of a learning health system, and standardization at the registry level would enable creation of data infrastructure to support multiple purposes (Figure 1). This data infrastructure could also serve as the foundation for learning health systems, quality improvement efforts, and value-based care programs.

The Outcome Measures Framework harmonization effort is particularly relevant as a model for the development of outcome measures for value-based care initiatives. Consider, for example, measurement of outcomes in depression. Depression is a major public health concern, affecting some 16 million adults and 3 million adolescents in the United States. Depression can reduce quality of life substantially and impair function at home, work, and school, resulting in a high economic burden. Many questions exist about how to improve patient outcomes in depression, including how to identify optimal first-line treatments and how to sequence treatments for patients who do not respond to the first treatment. Yet, research is complicated by the different definitions of key outcome measures, such as remission. Remission typically is defined using a validated instrument for measuring symptom severity, but different studies use different instruments and different time frames, making comparisons difficult. In addition, many of the instruments used in research settings are not used widely in routine clinical practice, making it challenging to compare the results achieved in a research setting to those seen in real-world settings. There is also a lack of consensus on what else to measure—for example, social functioning, cognitive functioning, and quality of life are all important to patients but are not routinely measured.5

The Outcome Measures Framework harmonization effort attempted to address these issues by building a minimum set of 10 harmonized depression outcome measures that could be captured across research and clinical care settings. A work group of 28 stakeholders representing patient registries, quality improvement efforts, payers, federal agencies, researchers, health systems, clinicians, and patient advocacy organizations reviewed different outcome measures definitions, identified a set of 10 broadly relevant measures, and agreed on a harmonized narrative definition for each measure. The harmonized narrative definitions were then mapped to standardized terminologies (eg, ICD-10, SNOMED [Systematized Nomenclature of Medicine]) to facilitate consistent extraction from electronic health records and other data collection systems. These measures were published in May 2020.5

Similar workgroups created minimum measure sets in the other condition areas selected for this project. By working across 5 clinical areas, AHRQ found that harmonization is feasible, even in clinical areas with multiple treatment pathways, and that the Outcome Measures Framework is an effective tool to facilitate harmonization efforts.

Moving Standardized Outcomes Into Practice

Development of standardized outcome measures is an important first step for building data infrastructure for research, value-based care, and other uses. Equally important is the subsequent step of implementing these measures in research and clinical practice settings. Over 120 stakeholders representing clinicians, researchers, health systems, professional associations, patient organizations, payers, federal agencies, and health information technology participated in the Outcome Measures Framework harmonization project. While they were enthusiastic about the standardized measures, they pointed to the need for more evidence on the value and feasibility of collecting the minimum measure sets. They also identified potential barriers to implementation, including the cost of modifying existing studies, questions about the feasibility of collecting the measures in routine clinical care, and the need for continuity with prior research.

To address these barriers and encourage adoption of the measures, AHRQ funded a new project to implement the standardized depression outcome measures in 2 patient registries and a health system setting. As part of this project, the registries will capture the additional data necessary to calculate the standardized measures, including the Patient Health Questionnaire-9 (PHQ-9), within a subgroup of pilot sites to assess feasibility and impact on practice workflow. The project also leverages an application integrated with the health system’s electronic health record to

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**Figure 1. Registries and the Learning Health System**

- **Track long-term patient outcomes**
- **Collect PROs**
- **Collect & transmit data for quality measurement, value-based care**
- **Provide tools to support quality improvement**

**Procedural Outcomes**

- **Data Collected Once & Used for Multiple Purposes**
- **Observe natural history of disease**
- **Assess effectiveness**
- **Meet post-marketing commitments**
- **Provide decision support at point of care**
- **Support reimbursement, accreditation, value-based care**

**Patient Outcomes**

- **Research**

**Quality Measures**

- **Clinical Practice**

**PROs = patient-reported outcomes.**

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provide measurement at the point of care and to provide an interface to send data to medical society managed registries.

The objectives of this project are to assess the feasibility of capturing the standardized depression measures using routinely captured clinical and patient-reported data and to examine the value of the measures for informing clinical decision making, supporting research, and ultimately improving patient care. This project is intended to create the foundation for a national data infrastructure to support patient-centered outcomes research in depression as well as other efforts focused on research, quality improvement, learning health systems, and value-based care. In this pilot phase, data will be used to examine whether patients with depression receiving care in the family medicine and mental healthcare settings differ in terms of demographics, severity of symptoms (as measured by the PHQ-9), frequency of PHQ-9 completion, and type(s) of treatments. In the future, the data infrastructure created by this project may be leveraged to address broader research questions, such as questions around treatment effectiveness and comparative-effectiveness, and to support measurement-based care in depression. While the potential role of measurement for value-based care in mental health has been well described, it is being underscored currently as telehealth and alternative approaches to care are implemented during the COVID-19 pandemic.

Next Steps
As our health system increasingly moves toward data-driven approaches to value-based care and quality improvement, standardization of outcome measures will be essential to support efficient capture of meaningful data and to enable comparisons of outcome measures across providers and across treatment and diagnostic options. The effort to develop and implement standardized outcome measures in depression should provide a roadmap for broader adoption of the depression measures and future efforts to standardize outcome measures in other clinical areas.

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Early Health Technology Assessment Advice: Opportunities to Achieve Collaborative and Efficient Dialogue

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By pursuing early health technology assessment advice, manufacturers can gain a better understanding of the requirements and receive trial-specific feedback, although internal expectations should be managed as the advice is non-binding and does not guarantee a future positive assessment.

Early health technology assessment (HTA) advice, also called scientific advice, is a formal process that allows manufacturers to gain nonbinding feedback from HTA bodies on clinical trials prior to the launch of a product or device (Figure 1). To submit an early HTA advice request, manufacturers must prepare and submit a briefing book, which requires substantial time and internal coordination to align on key questions and position statements. Briefing book requirements include aspects such as disease background and current treatments, product information, and the planned study design.

What Is Early HTA Advice?
Early HTA advice varies because it is available at the national, HTA and regulatory, or multi-HTA level. At the national level, European Union (EU) countries such as France, Germany, and the United Kingdom offer formal national procedures for market-specific advice. At the HTA and regulatory levels, parallel consultations with the European Medicines Agency and HTA bodies offer joint regulatory and HTA advice. At the pan-EU level, the European Network for Health Technology Assessment (EUnetHTA) multi-HTA early dialogues allow manufacturers to get feedback from more than one market.

Early HTA advice also varies by market in terms of types of advice offered, product requirements, and advice fees. The UK’s National Institute for Health and Care Excellence (NICE), the French Authority of Health (HAS), and Germany’s Federal Joint Committee (G-BA) all have formal national HTA advice, joint regulatory advice, and EUnetHTA advice offerings. NICE and the G-BA also offer joint advice with local regulatory agencies (ie, Medicines and Healthcare Products Regulatory Agency, Federal Institute for Drugs and Medical Devices, Federal Institute for Vaccines and Biomedicines). NICE also offers joint

Figure 1. Considerations for Manufacturers Seeking Early HTA Advice
advice with Canadian Agency for Drugs and Technologies Health (CADTH) and can advise on modeling questions (i.e., PRIMA [Preliminary Independent Model Advice]). At the current time, NICE offers the most customizable option with higher fees, whereas HAS requirements are stricter, but advice is free.

Benefits of Seeking Early Advice as a Manufacturer

By seeking early advice, manufacturers can gain deeper insight into market-specific HTA requirements and how these may differ based on the product situation. Early advice requires internal manufacturer coordination between global, regional, and local teams to assist in the development of a global briefing book for submission. The manufacturer will also gain specific feedback on trial design-related aspects such as patient population, comparator, and endpoint selection, which ensures that if feedback is implemented, the phase III trials are appropriately designed to meet HTA expectations. This feedback provides expectations for the future evaluation of a product that can help manufacturers understand key potential HTA drivers and detractors to help strengthen the future dossier. Finally, engaging as early as possible with HTA bodies highlights an openness to collaboration.

On two recent occasions, early HTA advice has proven to be beneficial for product assessment. In the case of Novartis’ Luxturna, the gene therapy benefited from early dialogue with NICE to secure their authorization in record time of 20 weeks (compared with the average of 38 weeks). In the first meeting with NICE’s evaluation team, clinical efficacy, cost-effectiveness, patient need, and service requirements were discussed. According to Meindert Boysen, director of the Center for Health Technology Evaluation at NICE, “The company’s willingness to work with [NICE] early and constructively has allowed [NICE] to publish guidance on a much faster timeline than normal which is good news for patients.” The evaluation process was streamlined, requiring less time to reach the final evaluation determination stage because neither a draft consultation or a second committee meeting was held.¹²

Novartis sought advice from NICE on early evidence generation for their collaboration with Innovative Medicines Initiative project PREFER, a preference study with chronic obstructive pulmonary disease (COPD) patients. The project aims to understand how patients cope with clinical burden associated with different COPD symptoms. Nigel Cook, head of Decision Support & Insights of Global Patient Access at Novartis, acknowledged that the early advice will “improve the design of the COPD patient preference study. Collecting certain outcome data alongside the patient preferences, one of the advice recommendations, will also help in correlating the preference results with current NICE processes for evaluating new treatments.”¹³ Four The feedback helped transform the study design and improve the quality of current processes.

Benefits of Offering Early Advice as a Payer

It is advantageous for both the HTA body and manufacturer to level-set expectations and achieve alignment as early as possible. A stronger future working relationship with the manufacturer can be established if advice recommendations are acted on. Payers will also gain an increased awareness of pipeline therapies and understand how the treatment paradigm may evolve in the next few years. Not only are there benefits to the payer in their dialogue with the manufacturer, payers can also gain perspectives from other payer stakeholders in joint or parallel consultations. In collaborative consultations, payer stakeholders can streamline their advice through a single process. For example, in response to NICE and CADTH’s collaboration to offer parallel scientific advice, Jeannette Kusel, director of NICE Scientific Advice, recognized that the “new collaboration with CADTH uses the synergies between the English and Canadian systems and...”
provides companies with comprehensive and practical advice from both countries through a single, streamlined process.\textsuperscript{5}

The Importance of Timing to Ensure a Successful Advice Process

Timing is key for ensuring a successful advice process, as manufacturers must determine the point where enough alignment is reached in the clinical development plan, but with enough time to act on the advice prelaunch. Early advice can be incorporated into the pivotal trial design-planning process, although if pursued too early, there may be internal disagreements on major trial design aspects. The window of opportunity typically occurs after the phase II trials have been conducted, but before the phase III trials have started. While abbreviated advice processes are available in some markets, such as NICE,\textsuperscript{6} a standard advice process can take around 6 to 8 months (Figure 2) due to the need to coordinate internally and externally.\textsuperscript{7,8}

Considerations for Manufacturers to Make the Most of Early HTA Advice

It is important that the manufacturer selects the appropriate type of advice, depending on manufacturer capabilities and markets of interest. By developing a global briefing book, local affiliates can pursue early advice on their market efficiently without exhausting local resources. Local team involvement is key, and briefing book materials typically need to be submitted in the local language. Within the briefing book, strong question development should be considered because early advice is only as beneficial as the questions that are asked. Additional expert input via market research can help refine the appropriate access questions. While early advice may resolve remaining strategic questions after a product’s access challenges and opportunities are well understood, it is not a means to identify these challenges and opportunities. Overall, both manufacturers and payers can work towards a streamlined process and seek early HTA and regulatory advice to help lower barriers to patient access. •

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Now more than ever, there is a pressing need for real-world evidence to inform decision making in this COVID-19-affected world. In this month’s Q&A, Jennifer Graff, PharmD, Vice President, Comparative-Effectiveness Research at the National Pharmaceutical Council in Washington, DC, looks at how real-world evidence is being used to give direction to patients, providers, payers, and policy makers.

VOS: Several individuals have offered opinions on what the rise of real-world evidence means for the pharmaceutical and vaccine industries. What is your perspective?

Graff: The rise of real-world evidence is a positive step forward for patient care and patients. Too often, patients and consumers do not know what to expect over the course of their disease, how treatments work for patients who look like them, or what the optimal treatment sequence is. When we spoke with representatives from patient organizations, we heard clearly that patient representatives were surprised that real-world evidence studies were not already deeply embedded in clinical care decisions. They recognized that high-quality studies using real-world data—when done with high-quality data and good research methods—can fill gaps in knowledge and inform routine care and coverage decisions.

In the past few years, the conversation has shifted. There is a broader understanding that real-world evidence can complement, not compete with, randomized controlled trials. Researchers have estimated that the use of real-world evidence could reduce trial costs between 5% to 50% to expedite safety monitoring and simplify trial and data collection.”
trials. The time and costs to answer the questions we—patients, providers, payers, policy makers collectively—need to know are too prohibitive not to use all high-quality and trustworthy evidence.

**VOS:** Do you see specific areas where real-world evidence has been more broadly accepted as a part of the research and development paradigm? Why do you think this is the case?

**Graff:** For the biopharmaceutical and vaccine industries, the rise of real-world evidence offers many opportunities to expand beyond the traditional use of real-world data for safety surveillance. Real-world data are used to identify potential drug or vaccine targets and pathways. Researchers have estimated that the use of real-world evidence could reduce trial costs between 5% to 50% to expedite safety monitoring and simplify trial and data collection. Real-world data are transforming clinical trial designs and accelerating trial recruitment to get new treatments to patients more quickly.

Within the clinical trial context, pragmatic studies combining randomization with real-world evidence sources have seen broader acceptance. For example, a pragmatic trial comparing paliperidone to traditional treatment among patients with schizophrenia and prior contact with the criminal system supported the product’s expanded indication. In oncology and rare disease development programs, historical control arms provide natural history comparisons for single-arm open-label studies. Once approved, value-based arrangements rely on quality real-world data to quantify treatment results and transform payment and reimbursement. While these benefits are significant for drug development, what is important to remember is that positive steps for patient care and patients are positive steps for the biopharmaceutical and vaccine industries.

**VOS:** Do you foresee any issues that could prevent its successful use?

**Graff:** There are multiple technical challenges with the collection, transformation, and evaluation of real-world evidence. However, we are learning that good data with thoughtful design and analysis yield similar results regardless of the sophisticated statistical manipulations.

The more intractable obstacles are the cultural and infrastructure challenges. Traditional research paradigms still exist in many research and development organizations. Clinical trials and real-world evidence are seen as separate, rather than complementary, designs. There are infrastructure challenges as end users cannot determine if the results of a real-world evidence study reflect a prespecified analysis or the most positive and impressive result. Finally, the demand for highly trained individuals to design and analyze high-quality real-world evidence studies exceeds the supply. These challenges can be overcome with education, tools, and training.

**VOS:** You have seen the use of real-world evidence become more prominent over the past several years, including in the National Pharmaceutical Council’s own research. Despite its increase in prominence, there still appears to be a lack of urgency with respect to its broad adoption and application in the healthcare sector.

**Graff:** Yes, real-world evidence has become more prominent. Is the adoption and application as swift and consistent across all decision makers as it could be? No, but there is some movement. For example, real-world evidence is cited more frequently in coverage decisions by US commercial health plans. In 2017, real-world evidence comprised 10% of all cited studies. In 2019, citations grew to 16% of all studies. This increase may be due to new treatments for rare and orphan diseases, where information may be more limited and real-world evidence relied upon more often. However, health plans are also becoming more familiar with real-world data and real-world evidence through more sophisticated uses, such as predictive modeling and value-based agreements.

Another area where adoption and application are lacking is the consideration of external control arms versus real-world data studies across the board. External control arms compare the results from historical or concurrent real-world data to the results from typically open-label, single-arm studies. Regulatory groups have shown willingness to use these real-world data to support product approval when traditional clinical trials would be difficult or unethical to conduct. Yet, health technology assessors and reimbursement bodies have been less willing to consider the same information when assessing value or applying add-on payments for these new technologies.

**VOS:** In recent years, a distinction has been drawn between regulatory grade real-world evidence and that used to support coverage decisions and guideline development in healthcare. Do you see this approach changing the threshold for the type of real-world evidence being used in coverage decisions and guideline development?

**Graff:** This is an important distinction and one we think about a lot. The US Food and Drug Administration (FDA) has been an important arbiter of truth. The agency’s use of high-quality real-world evidence could accelerate the adoption (or rejection) of real-world evidence by other stakeholders. As clinical guideline bodies and health plans must make hundreds of decisions a year, it could be easy to limit their use of real-world evidence to regulatory-grade evidence. For example, some health plans use journal tier as a proxy for study quality and have noted they only consider studies published in higher-impact or tier journals. But as we have seen in a recent systematic review, journal impact factor cannot be relied upon as a surrogate for study quality.

We also worry that very narrow use or very stringent requirements for regulatory-grade real-world evidence...
considered by the FDA will have implications for other stakeholders. There are opportunities for all federal healthcare programs—not just the FDA—to consider how real-world evidence could guide decision-making.

**VOS:** What do you see as the primary difference between the two approaches?

**Graff:** The key difference is the level of uncertainty each group (eg, regulators, clinical guideline bodies, health plans) is willing to tolerate. Regulatory decisions and the evidence underpinning these decisions have little room for uncertainty. For example, best correct-distance visual acuity is a meaningful endpoint for regulatory decisions but may be less relevant for health plans that are trying to slow vision loss. The endpoints often used in regulatory decisions are helpful but insufficient for coverage decisions.

Second, the FDA requires randomized controlled trials to meet certain data quality checks such as data completeness, confirmation, and provenance. For clinical trials, the study protocol and analysis plan are prespecified and shared to ensure the research methods are transparent. These elements are just as important for regulatory-grade real-world evidence. For reimbursement-grade real-world evidence, these studies should use high-quality data and have prespecified hypotheses and be transparent; they are likely to require fewer checks and balances than regulatory-grade real-world evidence.

Finally, the trial populations are often narrowly defined for regulatory studies. Regulatory-grade real-world evidence is likely to mimic hypothetical trials and will likely exclude the patient populations considered by clinical guidelines and coverage bodies. As we gain clarity on regulatory-grade real-world evidence, similar conversations are needed to define and develop reimbursement-grade real-world evidence.

**VOS:** Do you foresee a shift in how evidence hierarchies address real-world evidence in their criteria moving forward?

**Graff:** Basing evidence hierarchies on the decision to be made, rather than on the studies and study designs, is a laudable goal. However, it may be a step too far. Evidence hierarchies currently allow groups to rely on study design alone, short-cutting the assessment of a study’s credibility or risk of bias. Even when groups shift towards “best available evidence,” they may use blunt assessment tools. For example, some assessment bodies only consider real-world evidence studies if they include certain outcomes or have a specific sample size. Over the past decade, the National Pharmaceutical Council, along with other groups, has developed tools such as the GRADE system, the CER (comparative effectiveness research) Collaborative questionnaire, and other tools to help end users assess an individual study’s credibility and bias. Using the totality of evidence from lower- and higher-risk studies, rather than only a subset of individual studies, helps improve the certainty of the final recommendations.

**VOS:** Do you foresee real-world evidence driving greater levels of collaboration between stakeholders (healthcare providers, payers, and policy makers)?

**Graff:** Absolutely. Collaboration will extend beyond the traditional stakeholders, providers, payers, and policy makers. Activated patient groups are eager to contribute data if they have clarity around privacy and ownership of data and offer opportunities for supplemental real-world evidence endpoints. I also expect we will see more collaboration across the biopharmaceutical and vaccine industries as more pragmatic and adaptive study designs are initiated to ensure more efficient trials and adapt to new treatment combinations.

**VOS:** If you were to project out 5 years, where do you feel the future of real-world evidence will be in the pharmaceutical and vaccine industries?

**Graff:** By 2025, the use of real-world evidence for approvals or supporting approvals should become less anecdotal and more routine. Regulatory-grade real-world evidence may be limited to certain disease contexts initially, but successful biopharmaceutical organizations will use real-world data to accelerate their product development across all therapeutic areas. Beyond the regulatory environment, I hope that the use of real-world evidence in clinical guideline development, and payment and coverage decisions will be less sporadic and more routine. This will require researchers to ensure that the quality of real-world evidence developed is based on reliable data, use credible methods, and be transparent in the process used.

Can this be accomplished in 5 years? That timing is aggressive. But we owe it to the patients who want to know what is most likely to work best based on their personal characteristics to try.

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**Martin Marciniak, PhD, is the Section Editor for the Q&A column.**
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