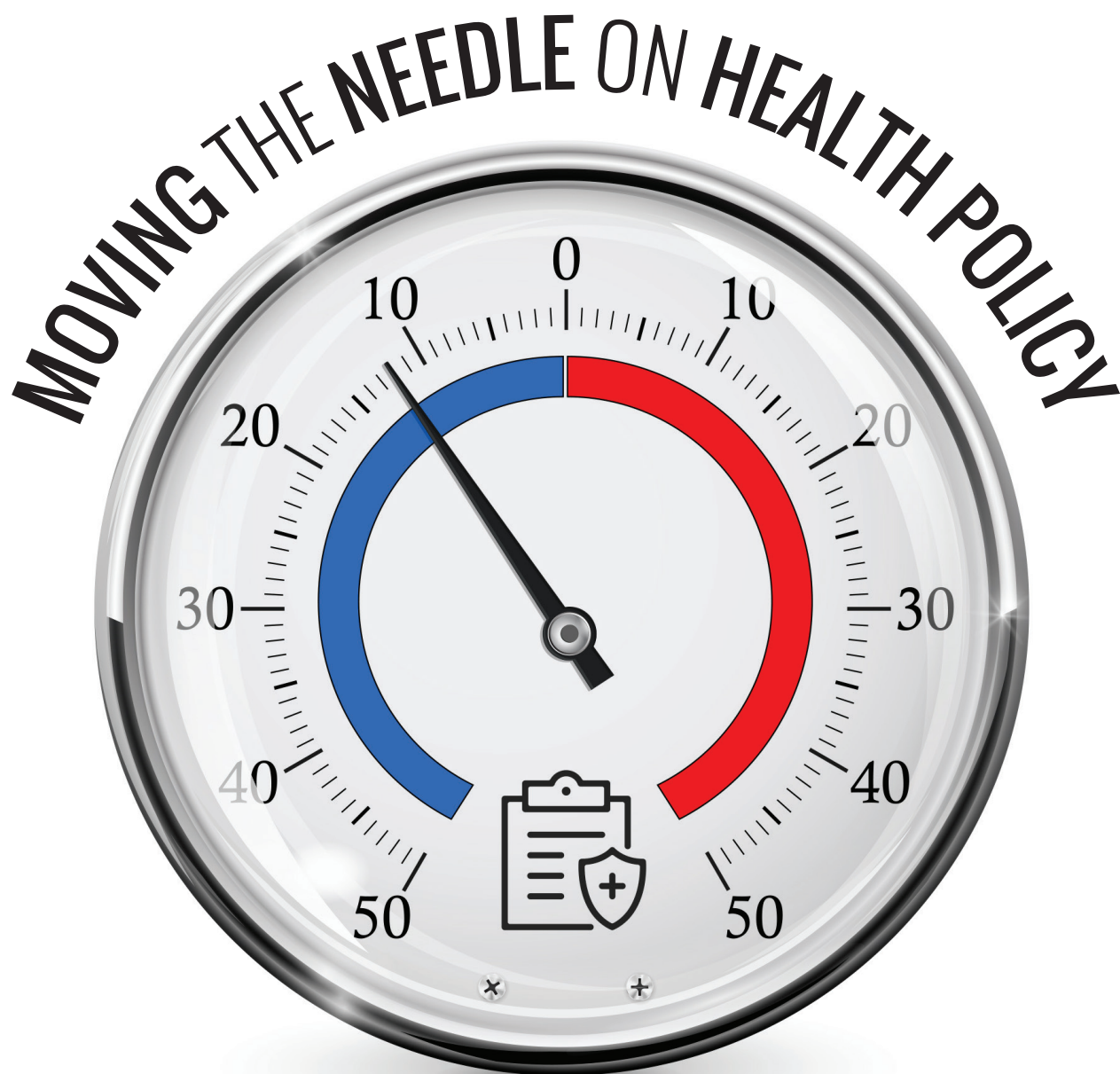


MARCH/APRIL 2022 VOL. 8, NO. 2

VALUE & OUTCOMES SPOTLIGHT

A magazine for the global HEOR community.



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VALUE & OUTCOMES SPOTLIGHT

MARCH/APRIL 2022
VOL. 8, NO. 2

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FROM THE EDITOR

Moving the Needle on Health Policy

Health policies—particularly policies related to public health—have undoubtedly and profoundly changed health status worldwide. From laws and regulations such as seat belt mandates to policies related to proper prescription and dispensation of and access to life-saving medicines (eg, vaccines), these policies have reshaped community consciousness of and greatly improved public health. Although in the best interest of the target population, health policy decisions can be extremely complex and are influenced by several social, scientific, economic, behavioral, and political factors. Choices in health policy can be biased—particularly during public health crises—as decision makers tend to rely on their instincts, anecdotal evidence, qualitative proof, and incomplete or uninterpretable quantitative outcomes. HEOR has a clear role in partnering with health policy makers to provide clear, unbiased, evidence-based analysis for data-driven decision making. Real-world evidence (RWE) and real-world data (RWD) are two key tools in the HEOR toolbox for providing clear, unbiased, and evidence-based recommendations to health policy makers.

Although traditional, randomized controlled trials (RCTs) are the gold standard for measuring clinical and patient outcomes, RWE and RWD are increasingly being applied in both healthcare and health policy decision making. RWE has the potential to allow us to assess the “known unknowns” of healthcare due mainly to the affordability of collecting immediate RWD, providing access to large sample populations that allows for more detailed and specific analyses, and better representing actual practice in the real world. This in-depth insight is very difficult to achieve with RCTs—where only the “known knowns” are more likely to be considered in a clinical trial design. The temporally expedient and accelerated nature of RWD can also direct rapid development of RWE to drive public health needs during dire and urgent medical crises, as was best demonstrated by the global health policy response to the COVID-19 pandemic.

Globally, RWE is being increasingly recognized and utilized by various health policy stakeholders including regulatory agencies such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). Agencies such as these are already relying on RWD and RWE for monitoring post-market safety and adverse events and making regulatory decisions. The 21st Century Cures Act passed by the US Congress in 2016 emphasized to federal agencies—primarily the FDA—the utility of RWD and the resulting RWE to support its regulatory decisions particularly in the approval of new indications for existing therapies. As an example, the FDA recently approved a new use for Prograf (tacrolimus)—an immunosuppressant originally approved for liver transplant patients—in adult and pediatric lung transplant patients based on an observational study providing RWE of its effectiveness. Currently, Prograf is the only approved drug for this population, illustrating the profound value that RWE can add to the lives of patients with unmet medical needs.

In addition to health policy makers, multiple stakeholders such as manufacturers, providers, payers, and even patients are leveraging RWE in unique and impactful ways. For manufacturers, RWE provides unparalleled insight into the prescribing of their drugs and use by patients. These companies are also utilizing RWD and RWE to enhance the design of their clinical trials and observational studies to demonstrate new and innovative treatment approaches for their products. Providers and other health-related care communities are using RWE to improve their delivery of care, support coverage decisions, and develop guidelines for clinical practice use. Such evidence is being utilized by payers to assess treatment outcomes, better inform their negotiations, and further support decision making in market access. Finally, patients themselves are collecting personalized RWD through health diaries, wearables, etc to better engage in their own healthcare by monitoring their treatments and progress toward their health goals while in the process collecting a personalized record of supplemental data that can be valuable in healthcare discussions with their providers.

Potentially, a real quantum leap in value for patients can be made in the medical “known unknowns” revealed through the collection, curation, and analysis of RWD to yield insightful RWE that can be leveraged by multiple stakeholders to improve health policy decisions. Collection of this data leading to unique evidence-based perspectives will unlock our potential to answer key societal and individual healthcare questions that were previously disregarded or—in some instances—inconceivable and thus change the nature of health policy worldwide. With the accelerated collection and vetting of tremendous amounts of health-related data from sources such as patient forums and social media, mobile devices, wearables, electronic health records, claims and billing activities, product and disease registries, and many other real-world data-rich resources, RWD and RWE is poised to make a tremendous—and perhaps unimagined—impact on our global health systems, health policy, and patient outcomes.

As always, I welcome input from our readers.
Please feel free to email me at zema.m.khan@hotmail.com.

Zeba M. Khan, RPh, PhD

Editor-in-Chief, *Value & Outcomes Spotlight*



ISPOR SPEAKS

Diversity's Role in Advancing HEOR Excellence: ISPOR's Women in HEOR Initiative

Betsy Lane, Senior Director and Chief Marketing & Communications Officer, ISPOR, Lawrenceville, NJ, USA

Why Focus on Diversity?

Research studies have continuously demonstrated that diversity of all types significantly improves performance and outcomes. ISPOR's mission to promote health economics and outcomes research (HEOR) excellence to improve decision making for health globally ties integrally to how diversity can have a positive impact on the quality of research and healthcare decisions. One way that ISPOR is responding is through its [Women in HEOR](#) initiative that rests on the foundation that fostering diversity in HEOR will not just promote equity, but also spur innovation, enhance research, and improve healthcare decisions.

McKinsey's research on diversity and performance is often cited and has routinely demonstrated that diverse executive teams financially outperform less diverse teams.¹ The 2020 report found that gender-diverse executive teams performed 25% better and ethnically diverse executive teams performed 36% better when compared to nondiverse teams. Additional detail on this research can be found in McKinsey's report, "[Diversity Wins: How Inclusion Matters](#)."¹

Much research also shows how women are underrepresented in science, technology, engineering, and mathematics (STEM) fields. Globally (averaged across regions), women accounted for less than one-third (28.8%) of those employed in scientific research and development across the world.² Additionally, the "leaky faucet" phenomenon occurs as women progress in their careers in which fewer and fewer women are represented at each step on the career ladder. Illustrating this is a study that examined women in economics at the top 20 European faculties in this field. This study found that women represented 35% of PhD students, but only 26% of academic faculty, and only 13% of full professors.³ Clearly, much work is needed to achieve gender parity.

Diversity at ISPOR

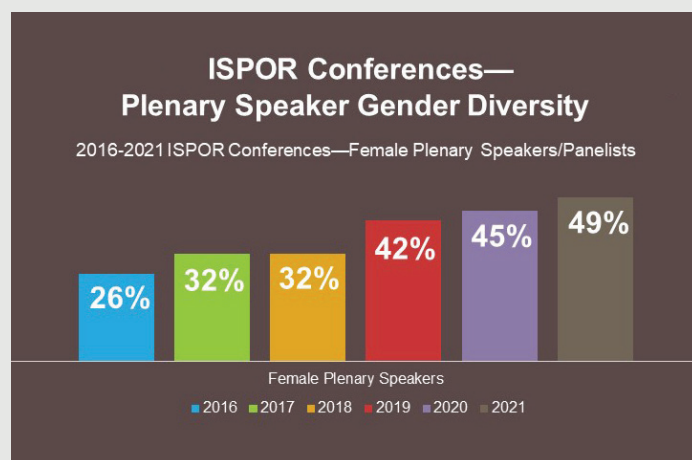
Lack of diversity is an issue that is pervasive, deeply entrenched throughout virtually all aspects of everyday life, and an issue that impacts essentially every sector and geography. ISPOR has been proactively addressing diversity for some time and it is one of the Society's organizational values that is outlined in its [Strategic Plan](#):

"We embrace diversity and inclusion in our membership and in all endeavors."

ISPOR is also committed to diversity of all types, as outlined in its diversity dimensions that include gender, career stage, ethnicity, race, education, sexual orientation, regional/geographic location, physical disabilities, religion, and more.

ISPOR's Diversity Impact

As ISPOR has been aiming to improve diversity and inclusion, its Women in HEOR group has been working to help capture and report on those metrics. Notably, the Society is actively striving to improve the gender diversity of its conference speakers, with significant progress made over the past 6 years. Illustrating this progress is the improved gender balance of invited speakers (plenary and spotlight sessions) at ISPOR's annual conferences. In 2016, only 26% of these speakers were women. In 2021, 49% of ISPOR's plenary and spotlight session speakers were women. ISPOR's Board of Directors has also long been a highly diverse board with its current 2021-2022 board at 50%/50% gender diversity and geographic representation from around the globe.



The Founding of Women in HEOR

The Women in HEOR initiative was founded by ISPOR's 2017-2018 President, Shelby D. Reed, RPh, PhD of Duke University. This initiative is one of Dr Reed's key achievements during her term as President and it speaks to her commitment both to women in the field and to excellence in research. Joining Dr Reed early in its initiation was Olivia Wu, PhD of the University of Glasgow. Today this initiative is co-led by Dr Wu and Julia F. Slejko, PhD of the University of Maryland.

The Women in HEOR vision was established at its inception and aims to:

- Support the growth, development, and contribution of women in HEOR
- Serve as a catalyst for women's leadership in the field
- Offer a platform for ISPOR women to collaborate, network, share, and mentor each other

Women in HEOR Events and Resources

ISPOR hosts Women in HEOR events at its 2 annual [conferences](#)—the Society's annual international conference and ISPOR Europe. When in-person conferences are held, events have included a conference session, a "Meet the Speakers" reception, and Dine Arounds. These events are designed to offer both educational content and the opportunity for attendees from a variety of career stages and disciplines to network. During the pandemic, virtual sessions have been offered. The [ISPOR Women in HEOR webpages](#) provide information on the initiative, including an introductory video about Women in HEOR and how to get involved. There is also a link to the initiative's [LinkedIn Discussion Group](#). The [Women in HEOR Resources webpage](#) makes resources available from past events as well as external resources that are related to the initiative's mission. Past sessions have included topics such as "[Adapting to the 'New Normal'](#)" and "[Unleashing the Leader Within You](#)."

Cool Guy Allies

It is important to note that all are welcome to support and participate in the Women in HEOR initiative. The initiative is open to everyone, not only women. Many men support Women in HEOR and are critical to achieving diversity and inclusion objectives both within ISPOR and outside of the organization. A number of prominent male ISPOR members publicly support the initiative and are deemed "Cool Guy Allies." In fact, the Society now offers conference "Cool Guy Ally" badge ribbons at its in-person conferences to be worn proudly by men who would like to publicly support Women in HEOR.

How To Get Involved

Women in HEOR welcomes all who support the advancement of women in the field to join in its events, participate in its LinkedIn Discussion group, and support the initiative overall.

- Become an [ISPOR member](#) (if you are not already a member)
- Visit the [Women in HEOR microsite](#) for information and resources
- Join the [Women in HEOR LinkedIn Discussion Group](#)
- Attend a Women in HEOR session at an [upcoming ISPOR conference](#)
- Join the conversation on social media and use key hashtags: [#WomenInHEOR](#) [#CoolGuyAlly](#) [#ISPORian](#) [#HEOR](#)

[LinkedIn](#) | [Twitter](#) | [Facebook](#) | [Instagram](#)

Additional information on ISPOR's broader diversity initiatives can be found at:

- [Diversity at ISPOR](#)
- [Diversity Policy](#)

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**What you need...
you know we got it:
Respect of the global
HEOR community.**



Leverage ISPOR's reputation and reach to maximize your visibility, impact, and connection within the HEOR field.



ISPOR NEWS

CHEERS 2022 Video Playlist: Topping the Charts in HEOR

Zeba M. Khan, RPh, PhD conducted an in-depth video interview with the Co-Chairs of the CHEERS 2022 Task Force Report, Don Husereau, BScPharm, MSc (University of Ottawa) and Michael F. Drummond, MCom, DPhil (University of York) to delve into how our readers and various HEOR stakeholders can use and apply the new CHEERS reporting standards in their work.

The videos in this section are presented in “bite-sized” pieces that provide key insights into what CHEERS is, who is the intended audience for these guidelines, and how this critical update can help improve healthcare decisions. This CHEERS 2022 video playlist will likely top the HEOR charts for years to come.

What is CHEERS?

The first CHEERS report was published back in 2013 and has become one of ISPOR's most highly cited Good Practices Reports. In short, CHEERS is an attempt to take reporting guidance that had existed in various forms and consolidate it into one useful guidance document that takes into account the latest thinking of how economic evaluations should be reported.



▶ Click here to watch the video

What precipitated this update?

There have been developments in the field of economic evaluation since 2013. Specific areas in particular that contributed to the update include: (1) the way that value is being characterized; (2) the growth of distributional cost effectiveness analysis, growing the use of these studies in decision-making settings; (3) an increased interest in transparency in research and in incorporating patients and the general public in the developments in health services research.



▶ Click here to watch the video

Why should Value & Outcomes Spotlight readers care?

Clearly the main audience is still the people that produce these studies, because if they don't report them correctly then we all lose out no matter what our perspective is. Economic evaluations, although they're often conducted and reported by specialists, have implications for everybody. CHEERS is designed to make sure that all the information that's there to help us understand is presented—but in a structured way—so that we can make quick sense of what a study says and what it doesn't say.



▶ Click here to watch the video

Who is this guidance intended for and will it help improve healthcare decisions?



▶ Click here to watch the video

What is ISPOR doing to help audiences apply CHEERS?

As a starting point, the explanation elaboration report was published in the January 2022 issue of *Value in Health*. There is also a new resource page on the ISPOR website (<https://ispor.org/cheers>) where people can find summaries, tutorials, templates, user guides, etc.



▶ Click here to watch the video

What would you like our Value & Outcomes Spotlight readers to do to advance the adoption and use of the CHEERS standards?

It's great to have this opportunity to speak to the readers of *Value & Outcomes Spotlight* because they're such a diverse group of people. I think we'd like to say to them all, "Think about what CHEERS means to you and how you can use it." If it's not touching all the buttons for you, give us some feedback and we maybe could develop some extra resources to support the diffusion of CHEERS.



▶ Click here to watch the video

Causal Inference in HEOR: Making Complex Decisions in a World of Imperfect Data

Signal IN BRIEF

- As the science of HEOR advances, researchers will have to turn to new research methods to interpret data and calculate cause effect relations
- Causal and counterfactual inference is a theory advanced by Judea Pearl, PhD, Professor of Computer Science and Director, Cognitive Systems Laboratory, Samueli School of Engineering, UCLA
- Pearl's work centers on how causal models interact with data and work in scientific applications today, spanning the subjects of selection bias, personalized treatment effect, causality in observational studies, and fusion of data from several sources (observational and experimental studies)
- While causal models are well known in the fields of computer science and artificial intelligence, as well as epidemiology, they are not taught in college statistics classes. However, they have substantial potential in economics and have begun to be more widely used in HEOR and HTA

According to Judea Pearl, PhD, Professor, Computer Science and Director, Cognitive Systems Laboratory, Samueli School of Engineering, University of California, Los Angeles, USA, even a 3-year-old has a remarkable understanding of causation.

As he explains in the first chapter of his book, *The Book of Why*,¹ humans' ability to reason retrospectively, imagine roads not taken, and compare the observed world with counterfactual alternatives, is something that even the most sophisticated artificial intelligence neural networks have not yet been able to achieve. However, he posits that there are ways machines and people "can represent causal knowledge in a way that would enable them to access the necessary information swiftly, answer questions correctly, and do it with ease, as a 3-year-old child can."

"Machine learning amplifies one little corner of human ability and this is to handle data, to store it, to collect it, to retrieve it, to answer questions about associations, to summarize data properly, to visualize data—all this is fine," Pearl says. "But the hard questions of causal thinking cannot be answered by machine learning alone, these must be handled by a smart symbiosis of causal models and machine learning. Whenever you do a causal inference exercise you get an answer that tells you where machine learning can be of help and how, so you can adequately divide the labor."

Pearl's causal metamodel is the "Ladder of Causation," which comprises 3 parts: the lowest level, **Association** (seeing/observing), entails the sensing of regularities or patterns in the input data, expressed as correlations. The middle level, **Intervention** (doing), predicts the effects of deliberate actions, expressed as causal relationships. The highest level, **Counterfactuals** (imagining), involves constructing a theory of the world that explains why specific actions have specific effects and what would have happened had those actions been different.

Causal Models and Healthcare

One industry that generates a lot of data is healthcare. According to [RBC Capital Markets](#), 30% of the world's data volume is being generated by the healthcare industry and by 2025 the compound annual growth rate of data for healthcare will reach 36%.

"Sorting through all of these data to derive information from them—especially in health economics and outcomes research (HEOR), in which much of the work is related to guiding patient-centered medical decision making and public health policy decisions—has to start with causal questions, using causal assumptions, and developing decision-analytic models," says Uwe Siebert, MD, MPH, MSc, ScD, UMIT - University for Health Sciences, Medical Informatics and Technology, Hall in Tirol, Austria, and Harvard Chan School of Public Health in Boston, MA, USA.

KEY TAKE-AWAYS

FOR HEALTHCARE INNOVATORS AND VALUE CREATORS:

- Although the principal concept of causal pathways had been introduced by the biologist Sewall Wright in 1921, it was forgotten until Pearl and colleagues in the 1980s developed a complete mathematical concept for causal diagrams.
- In 1999, causal diagrams were introduced to epidemiology and health sciences in a pivotal paper, "Causal diagrams for epidemiologic research," by Greenland, Pearl, and Robins.
- It was almost 15 years after Robins developed a new causal analytic approach in epidemiology (1986), when then-doctoral candidate, Siebert applied this method to real data. Siebert, Hernán and Robins published the first application of the parametric g-formula in a medical decision-making conference proceeding in 2002.
- It took a decade more for the pharmaceutical industry to become aware of g-methods when g-methods were successfully applied in HTA in Europe.
- Today, the main challenges in developing causal inference methods and applying them in HEOR and HTA are, first, adopting the query-based philosophy of causal inference methodology and, second, understanding which methods work best in which situation and how they can help us overcome obstacles and impediments that held us back for decades.
- Emerging causal inference tools promise to revolutionize the industry—reducing bias, enhancing evidence synthesis, and informing personalized medicine.

Causal models are needed because often it is impossible to run real-time experiments assessing long-term consequences that affect human individuals and populations. "There are of course, limitations and strict ethical rules about performing experimental clinical studies," Siebert says, adding that trying to run experiments on patient-relevant outcomes in real time is also problematic, especially in an ever-shifting environment such as the COVID-19 pandemic. "What if we treat, what if we don't treat, what if we start treatment early or start late? What if you wear masks, do COVID tests, or close schools? And what if not? We likely can't run experiments for all these decisions because by the time we get the results, it may already be too late for many of these decisions."

Siebert says another reason why causal inference is important in health decision science, and HEOR especially, is the fact that we live in a world with imperfect data, but decisions must still be made—with the goal of gathering further evidence to improve these decisions. The causal diagrams developed by Pearl and others combined with evidence-based causal decision analysis allow temporary decisions to be made based on the best evidence available at a given time, and more data can be filled in later once additional evidence is generated. "In health economics, we have a formal framework called value-of-information analysis that guides the efficient collection of further evidence and tells us when evidence is enough," Siebert says.

The Current State of Causal Modeling in HEOR

Although causal modeling has been around for decades, its penetration into healthcare and HEOR has been slow. As Siebert explains, the principal concept of causal pathways was introduced by the biologist Sewall Wright in 1921 and was forgotten until Pearl and his colleagues in the 1980s developed a complete mathematical concept for causal diagrams. In 1999, causal diagrams were introduced to epidemiology and health sciences in a pivotal paper, "Causal Diagrams for Epidemiologic Research."²

One of the authors, Harvard Professor James Robins' causal computation method, the "g-formula," had been developed in 1986,³ but it was almost 15 years later when Robins asked his then-doctoral candidate, Siebert, to apply this method to real data. Siebert published the first application of the parametric g-formula in a medical decision-making conference proceeding in 2002.⁴ It took a decade more (2012) for the pharmaceutical industry to become aware of g-methods, when g-methods were successfully used in health technology assessment (HTA) in the United Kingdom to adjust clinical trial data for treatment switching—and the drugs under investigation received reimbursement.

Anecdotally, Pearl and Robins have translated the g-formula into a graph-based sequential back-door formula, so that it could serve researchers who find graphs a convenient way of conveying scientific knowledge.⁵

Pearl believes that one of the reasons that causal thinking has not gained more ground as it definitely should in some sciences is a difficulty with language. "The language of causal thinking is not being taught in school. In Statistics 101, you wouldn't even be allowed to say the word 'cause,'" he says. "The textbooks, they warn you against stating causal assumptions. Or look in the index of every textbook in statistics, you wouldn't find 'causal effect' there, or any notion that is inherently causal."

Students coming from a statistics background believe that statistics is the language of science. "Means, variance, regression coefficients, confidence intervals, testing of hypotheses, things of that sort—this is what they take to be the language of science. But it is not!" Pearl says. "Science speaks cause and effect. And it takes generations to undo this deeply entrenched paradigm."

Today, according to Siebert, one of the main tasks in applying causal inference methods in HEOR and HTA is understanding which analytical method works best for which type of research question, and recommending what additional evidence should be generated. This will take time, although epidemiology, which is related to HEOR, has developed methods for causal data analysis that can be adopted.^{6,7}



"In any science, not just in medicine and health science, it may take decades after some knowledge has been generated or created, or a particular method has been developed, until it is known in the broader community in a field"

— Uwe Siebert

Read more about past *Signal* events in *Value & Outcomes Spotlight*

- ISPOR Generates a Signal for Transmitting Innovation
- From Measuring Costs to Measuring Outcomes: Revamping Healthcare at a System Level
- Beyond Cost-Effectiveness: Defining and Mapping Out Innovation at NICE
- Looking at the Downstream Value as Investment in Digital Health Increases

For more information and to register

www.ispor.org/signal

About the author

Christiane Truelove is a freelance medical writer based in Bristol, PA.

"In any science, not just in medicine and health science, it may take decades after some knowledge has been generated or created, or a particular method has been developed, until it is known in the broader community in a field," Siebert says. "I'm now old enough to be able to testify that this is definitely true in health sciences, including HEOR. And once the methods are known, it may take another 1 to 2 decades to try them out in routine settings, and move up the learning curve until we are experts—and we're not there yet. This is true for many clinical procedures and health technologies, but it's also true for analytic methods. Causal methods must be applied to the real, routine, imperfect, 'dirty' data—a nicer term is 'real-world evidence'—to gain experience with them and understand the strengths and limitations and when we should use them and when not, and when we can base decisions on the data available and when we still must stick to experiments such as randomized controlled trials."

Pearl adds that, even if HEOR and HTA use randomized controlled experiments as the gold standard study design, the tools that are currently emerging from causal inference promise to revolutionize the industry. Examples are tools for recovering from 'sample selection bias', coherent aggregation of findings from several heterogeneous trials, and, most excitingly, methods of informing personalized decision making.⁸ "Truly personalized medicine, I dare say, is much closer to reality than most researchers imagine," said Pearl. Although it has been decades since Robins' and Pearl's groundbreaking papers, Siebert believes that causal modeling in HTA and HEOR will progress faster if there are others willing to be trailblazers and apply the theories to their work. He says the support of ISPOR is crucial. "We are still on the steep part of the learning curve increasing our experience with each application. I think this is now our most important job and we should work together across scientific disciplines. There's a lot to be done."

Pearl presented basics about causal inference, moderated by Siebert, in ISPOR's January *Signal* episode, "The New Science of Cause and Effect: Causal Revolution Applied."

The ISPOR *Signal* Series

ISPOR started the *Signal* program to bring a broader understanding of innovation (beyond product innovation), with the goal of putting these issues front and center for the HEOR community. Each episode in the series is a self-contained installment and not dependent on the previous episodes; however, all of them are connected by an intent to look at the concept of innovation and experience with it from different groups of healthcare stakeholders, building foresight into how these innovations might impact healthcare decision making in the next decade.

"The next installment in the *Signal* series, "New Analytical Approaches to 21st Century Challenges," will be May 16. This episode will focus on envisioning and discussing the approaches needed to analyze the behaviors that are generated by the myriad interactions of billions of people at timescales ranging from nanoseconds (as in computer trading) to millennia (as in evolution). We will cover this episode more in-depth in a future issue of *Value & Outcomes Spotlight*.

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HEOR NEWS

1 How Strengthened Political Engagement Can Lead to Improved Health Outcomes in Africa (Brookings)

Brookings highlights a section of its Foresight Africa 2022 report, sharing hopeful statistics such as up to 95% of African countries have developed policies and plans on medicines, over 90% on blood safety, and 85% on traditional medicine.

[Read more.](#)

2 Infectious Disease Outbreaks Highlight Gender Inequity (Nature Microbiology)

The Ebola and COVID-19 outbreaks in Africa revealed a much higher vulnerability in women when it comes to the indirect health, social, and economic consequences of such health crises according to the authors of a new paper. The authors call for health systems and communities in these countries to address these gender inequity problems before a future outbreak.

[Read more.](#)

3 Climate Change 2022: Impacts, Adaptation, and Vulnerability (IPCC)

One of the areas of focus in the Intergovernmental Panel on Climate Change Sixth Assessment Report is the impact of climate change on health and the news is not good.

[Read more.](#)

4 Commonwealth and WHO to Strengthen Cooperation on Health, Including Access to Vaccines (WHO)

The Commonwealth Secretariat and the World Health Organization (WHO) have signed a Memorandum of Understanding committing to strengthening their collaboration on a broad range of public health issues of particular concern to Commonwealth member states and governments, such as the response to the COVID-19 pandemic, vaccine equity, advancing universal health coverage, and building resilient health systems.

[Read more.](#)

5 It's Time to Champion Health System Resilience (AstraZeneca)

Leon Wang, Executive Vice President, International, AstraZeneca, discusses how the company is working with tech companies around the world, including in many low- and middle-income countries, on innovative and digitally led approaches to improve access to healthcare and clinical trials for noncommunicable diseases such as diabetes, chronic lung illnesses, cancer, and heart disease.

[Read more.](#)

6 Taking Stock of Medicare Advantage: Choice (The Commonwealth Fund)

As the average Medicare beneficiary in the United States faces the prospect of choosing from among 39 Medicare Advantage plans. Experts say most beneficiaries aren't making informed or active decisions, picking plans based on advertising, word-of-mouth, or brand loyalty, and staying with those plans year after year, even if another plan would better serve their interests.

[Read more.](#)

7 Egypt Screens 75K Babies for Genetic Diseases in 7 Months (Egypt Today)

The Ministry of Health and Population has screened 75,000 babies for genetic diseases such as congenital hypothyroidism, hemolytic anemia, congenital adrenal hyperplasia, cystic fibrosis, and hereditary hyperlipidemia since the launching of the presidential initiative on July 13, 2021.

[Read more.](#)

8 HIV Preventive Care Is Supposed to Be Free in the United States. So, Why Are Some Patients Still Paying?

Under provisions of the Affordable Care Act, the decision to rate pre-exposure prophylaxis as an effective preventive service triggered rules requiring health insurers to cover the costs. Insurers were given until January 2021 to adhere to the ruling, yet patients across the United States are being assessed thousands of dollars for drugs, quarterly lab tests, and doctor visits.

[Read more.](#)

9 Can the Population Health "Fantasy Equation" Be Solved? Does It Need to Be? (Health Affairs)

David Kindig and John Mullahy ponder one of the biggest questions when it comes to public health: whether there is a way to balance out the elements of the complex model of looking at population health to come up with precise answers of where money should be spent. In the end the authors say, "Robust estimates of directions and orders of magnitude may be just as important in serving decision makers as precise but unreliable findings."

[Read more.](#)

10 xCures and BioSpark Partner to Boost Real-World Oncology Data Offerings (Newswires)

xCures Inc and BioSpark Inc have formed a strategic partnership to harmonize and commercialize a joint oncology real-world data offering, which they say unlocks new insights into the treatment and outcomes of patients with cancer through a novel dataset spanning 40,000+ patients.

[Read more.](#)

FROM THE JOURNALS

Investing in Healthcare Interventions: Finding a Common Threshold

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

The use of cost-effectiveness thresholds for evaluating health interventions in low- and middle-income countries from 2015 to 2020: a review

Kazibwe J, Gheorghe A, Wilson D, Ruiz F, Chalkidou K, Chi YL

Value Health. 2022;25(3):385–389.

<https://www.valueinhealthjournal.com/>

When investing in healthcare interventions, decision makers apply multiple criteria,¹ including the relative cost-effectiveness of different investment options (ie, the incremental cost-effectiveness ratio [ICER]). The ICER, estimated for various health-effectiveness metrics such as life years gained, quality-adjusted life years gained, or disability-adjusted life years avoided, etc² is then compared against a cost-effectiveness threshold (CET) and a judgment about the intervention being cost-effective is made. The threshold would generally reflect healthcare budget constraints in the given country.

In low- and middle-income countries (LMICs), the ICER is preferably measured as cost per disability-adjusted life years avoided.³ A CET standard for LMICs of 1 to 3 times the gross domestic product (GDP) per capita was proposed as a rule of thumb by the World Health Organization in 2001.⁴

In India, with a GDP per capita estimated at about \$7000,⁵ implementing a new healthcare intervention is deemed cost-effective if, for each avoided disability-adjusted life year by the new intervention, society spends less than \$21,000 over a given time horizon. In comparison, the threshold in European countries is set between €20,000 and €50,000, compared to the mean GDP of €40,000 of the 27 European Union member states.⁵

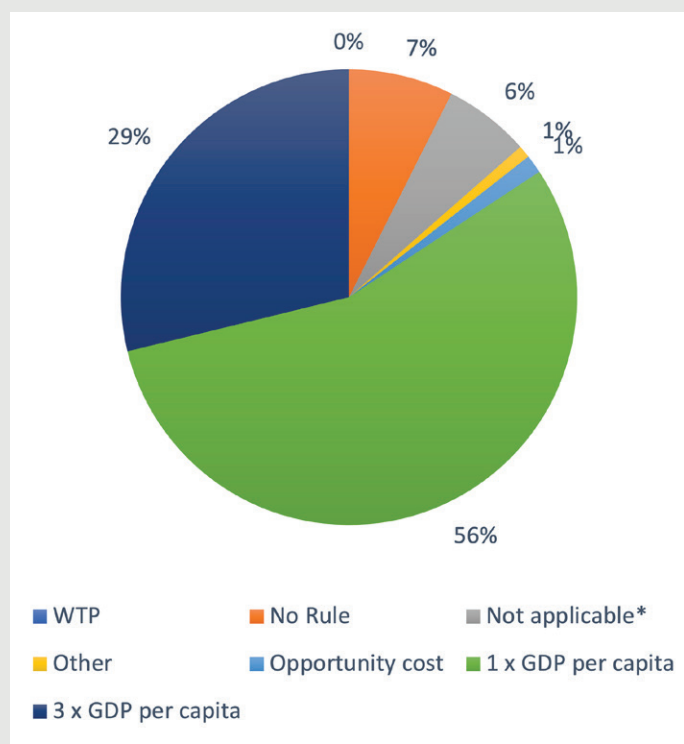
Estimating a threshold based on GDP per capita has long been criticized as being high and not reflecting healthcare budget constraints and opportunity costs of an intervention in LMICs.⁶ In this context, the authors set out to investigate the usage of thresholds based on GDP per capita in LMIC studies in recent years and the relationship between recommendations by the authors and the threshold applied.

The authors searched interventions and studies in the Global Health Cost-Effectiveness Analysis Registry⁷ from January 2015 to January 2020, selecting LMICs studies

using cost per disability-adjusted life year as an ICER metric and extracted the type of threshold used and the conclusion on the cost-effectiveness of interventions.

Overall, 713 healthcare interventions reported in 230 studies were identified, most of which were conducted in sub-Saharan Africa and South Asia. About half of the 230 selected studies compared preventive healthcare interventions: 26% for immunization, 15% for screening, and 7% other public health. Although the proportion of prevention in developed countries is unknown, assessment of technologies to prevent diseases seems to represent a significant amount of the research in the cost-effectiveness fields for LMICs. This is consistent with the assumption that LMIC societies have a propensity to invest in healthcare interventions that prevent the congestion of healthcare resources such as nurses, physicians, hospital beds, material and medication stocks/supply, etc. Therefore, opportunity costs are also considered when defining thresholds for cost-effectiveness as highlighted by the authors.

Figure 1. Distribution of studies according to the type of CET.

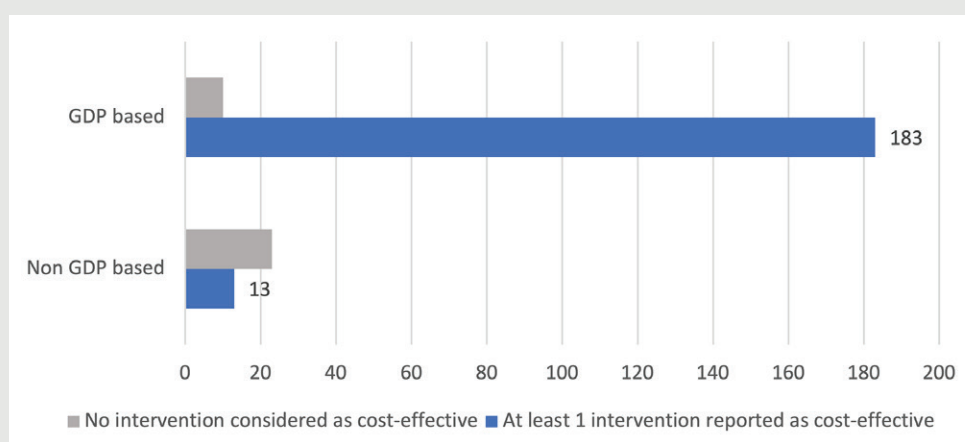


*Not applicable includes the following: cost saving (4.4%), dominant (1.3%) and dominated (0.4%). CET indicates cost-effectiveness threshold; GDP, gross domestic product; WTP, willingness-to-pay

Thresholds identified in the paper were classified into 3 categories: (1) GDP-based thresholds, which equal to 1 to 3 times GDP per capita in the country, (2) opportunity costs thresholds, which equal to 0.5 GDP per capita, justified as being an appropriate measure of opportunity costs^{8,9} and, (3) willingness-to-pay thresholds, which represent the less explicit yet more comprehensive category of society's valuation of healthcare benefits.

Of the 230 identified studies, 80% use the World Health Organization's GDP based threshold, as illustrated in **Figure 1**. Besides, as illustrated in **Figure 2**, 94% of the studies using a GDP-based CET (ie, 1 to 3 times the GDP per capita as threshold) report at least 1 healthcare intervention as being cost-effective, versus 36.1% of the studies using a non-GDP-base threshold (ie, opportunity cost, CET, or other).

Figure 2. Number of studies by CET type and conclusions on cost-effectiveness.



CET indicates cost-effectiveness threshold; GDP, gross domestic product

The 1-3 GDP per capita as a CET threshold to conclude the cost-effectiveness of healthcare interventions is still widely in use in published LMICs studies, despite previous criticisms about its appropriateness and warnings that application of such thresholds cannot appropriately prioritize healthcare interventions using cost-effectiveness in LMICs.

Clearly, publications do not reflect the actual reimbursement/adoption decisions in these countries and the role of cost-effectiveness analyses may vary in

healthcare decision making. However, further research would be required to identify the appropriate thresholds for each LMIC to ensure the credibility of health economic research for these geographies, and hence their usefulness for decision making. Readers of this article will receive an overview of previous literature on this topic of thresholds in LMICs, the cost-effectiveness analyses published for these countries and will understand why it is important to carefully consider the threshold to be used to make conclusions about cost-effectiveness of therapies, instead of automatically applying previously used thresholds.

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ISPOR NEWS

Benefits and Challenges of Performance-Based Managed Entry Agreements: Report From an ISPOR Payer Summit

Brian O'Rourke, PharmD, Chair of the ISPOR HTA Council, Ottawa, Ontario, Canada; Mark Trusheim, MSc, NEW Drug Development ParadIGMs, Massachusetts Institute of Technology, Boston, MA, USA; H. Arturo Cabra, MSc, ISPOR, Lawrenceville, NJ, USA

As more innovative therapies for life-altering and life-threatening diseases enter the global marketplace, the clinical and financial uncertainty associated with the new treatments presents a major challenge for decision makers. An increase in accelerated regulatory approvals and high costs for many new treatments amplify the challenge. Performance-based managed entry agreements can help manage that risk for all stakeholders and so promote appropriate and timely patient access to promising therapies.¹ However, payers continue to assess the benefits and challenges of performance-based contracting. For example, payers have expressed concerns regarding their complexity and administrative burden, and questioned if the financial rewards justify those added costs.

In April 2021, ISPOR sponsored a virtual payer summit to provide a forum to discuss the benefits and challenges of performance-based managed entry agreements, to identify efficient approaches to develop and scale up these types of agreements, and to identify best practices in their development and implementation. The ISPOR Payer Summit attracted over 60 participants. To ensure perspectives from multiple stakeholders were being addressed, the summit included representatives from health technology assessment (HTA) agencies, the pharmaceutical industry, patient groups, and academia as well as representatives from public and private payers in North America and Europe.

The summit consisted of 2 phases. Phase 1 involved a series of short presentations about the benefits and challenges of implementing performance-based agreements. Phase 2 consisted of breakout sessions to address specific topics and strategies to capitalize on the benefits of performance-based managed entry agreements. The summit was organized by the ISPOR HTA Council and moderated by Mark Trusheim, MSc, Strategic Director, NEWDIGS and Visiting Scientist, Massachusetts Institute of Technology, Cambridge, MA, USA.

Presentations

Martin Wenzl, PhD and Suzanne Chapman, health policy analysts at the Organisation for Economic Co-operation and Development Directorate for Employment, Labor and Social Affairs, summarized the results of a survey and publication on performance-based managed entry agreements for new medicines.² The work included assessing the effectiveness of performance-based managed entry agreements in achieving their stated goals and identifying good practices and opportunities for improvement. Chapman pointed out that patient-level "Payment by Result" and population-level "Coverage with Evidence Development" were the most common

performance-based agreement designs. She explained that most of the agreements to date place financial objectives at the forefront, leaving uncertainty around product performance in the shadow. Chapman emphasized that most concerns associated with managed entry agreements stem from their limited ability to reduce uncertainty regarding product performance due to data quality or methodological issues; challenges encountered during coverage-associated decision making; high levels of confidentiality that is a barrier to independent evaluation; and administrative burden, particularly related to data collection and analysis. Chapman pointed out that performance-based managed entry agreements should be reserved for specific situations. They should be designed to better address uncertainties and they should promote transparency of the process and on-product performance. Detlev Parow, PhD, Head of the Department of Medicines,

Performance-based managed entry agreements should be reserved for specific situations. They should be designed to better address uncertainties and they should promote transparency of the process and on-product performance.

Therapeutic Appliances and Remedies, DAK-Gesundheit, Hamburg, Germany, provided an overview of the German healthcare system and explained that Germany does not use managed entry agreements; however, they do use a form of selective contracting for one-time therapies that closely resembles the managed entry agreements process. "These products have mostly weak evidence at the time of launch, but they have very high promise or expectations. They are supposed to be a game changer cure for previously untreatable conditions." He pointed out that there are generally no entry barriers for pharmaceutical therapies in Germany as medicines can be launched immediately after regulatory approval. During the first year of market access, the product undergoes a health technology assessment by Germany's Institute for Quality and Efficiency in Health Care to estimate its added benefit when compared to the current standard of care. He emphasized that due to the incredibly high price point with many new medicines, payers have a multitude of concerns, including those of patient benefit. To address these concerns, Germany is piloting a new "Pool of High-Risk Patients" program in which patients' healthcare costs beyond a certain threshold are shared among all payers, thus relieving the financial burden of a single healthcare insurance company.

Donna L. Sullivan, PhD, Chief Pharmacy Officer, Washington State Prescription Drug Program, Olympia, WA, USA, shared the US payer perspective. She highlighted some of the barriers and challenges that US payers face when considering the use of managed entry agreements. For example, under the Medicaid Best Price program, manufacturers are required to report their average manufacturer price to the Centers for Medicare and Medicaid Services (CMS), which in turn sets the rebate for all Medicaid programs. “Manufacturers have been hesitant to enter into outcomes-based agreements with commercial payers in the United States because it is not clear how that would impact their average manufacturer’s price and how it would then be reported to the CMS.” However, the CMS will be introducing substantial changes to their programs by distinguishing between the average manufacturer price for commercial purchasers that enter into outcomes-based agreements, and those who do not. This will create more opportunities for commercial outcomes-based agreements in the United States. Additionally, Sullivan pointed out that smaller purchasers experience the greatest challenges as they often lack in-house expertise for negotiations, data collection, and analysis. This could be averted by introducing analytic work-related cost-sharing between the manufacturers and the purchasers so that purchasers can utilize performance-based managed entry agreements with a better return on investment.

Trust and collaboration between payers, providers, and policymakers is essential to address the challenges of significant variation in policies, guidelines, and regulations globally.

Indranil Bagchi, PhD, Senior Vice President and Head, Global Value and Access, Novartis, Switzerland, provided a perspective from industry using the current and future landscape of cell and gene therapies as an example. He emphasized that while there are fewer than 10 approved cell and gene products today over 1000 are in the pipeline, and the US Food and Drug Administration expects that by 2025 they will be approving 10-20 cell and gene products annually. To better prepare for this influx of novel therapies, the needs and goals of each stakeholder must be considered. Bagchi presented Novartis’ experience with bringing cell and gene therapies to the global market via managed entry agreements and outlined multiple pathways through which these products have been brought to market. Additionally, he noted that trust and collaboration between payers, providers, and policymakers is essential to address the challenges of significant variation in policies, guidelines, and regulations globally.

Results From the Breakout Sessions

The participants at the summit were divided into 6 breakout groups to discuss 3 separate topics associated with performance-based managed entry agreements implementation. Two groups focused on the types of products suitable for performance-based contracts, 2 groups discussed implementation barriers and opportunities to scale up performance-based contracting, and 2 groups reviewed best practices by highlighting some successful and unsuccessful examples of performance-based managed entry agreements.

Results From the Groups Discussing Product Suitability

Both groups pointed out that rather than identifying specific product classes or diseases, it is more important to consider characteristics of a particular technology or condition that might make it a suitable candidate for performance-based managed entry agreements. Most importantly, the characteristics of the condition itself should be considered. Products most suitable are those that could benefit patients suffering from life-threatening or severely debilitating conditions, particularly when no other viable treatment options exist. Other characteristics include high burden conditions or conditions that pose a severe health risk if immediate access to treatment is delayed. Additionally, technologies with high budget impact or exceedingly high costs should be considered. These types of drugs or technologies often offer theoretical efficacy and promise clinical benefits at product launch, but they typically enter the market with limited evidence and high uncertainty about the degree and durability of response. To minimize the clinical and financial uncertainties of the product and to demonstrate its value during the term of a performance-based contract, the groups proposed that centralized, standardized, measurable, and patient-focused data endpoints and outcome metrics should be established for product classes and therapeutic areas.

They also pointed out that products with existing evidence that have demonstrated the clinical and economic benefits of a treatment would not be good candidates for performance-based managed entry agreements. Additionally, products targeting health conditions with a lower burden of illness and relatively low health risk associated with delaying access should not be prioritized for these types of contracts. From a value standpoint, products with an unclear or low value proposition as well as products with marginal benefits are not considered good candidates. Finally, it was suggested to exclude products for conditions where outcomes are poorly defined or hard to measure as well as products where multiple competitors are available or soon to be launched.

When patients are included in the development of the agreement, meaningful outcomes and key decision points can be better incorporated into it.

Results From the Groups Discussing Barriers and Opportunities

Building on the first discussion, these groups also emphasized the high uncertainty around data collection and key outcome metrics as one of the major barriers to decision making and successful performance-based managed entry agreement implementation. They pointed out that the selected outcomes should be meaningful for patients, clearly defined, easily measurable, and potentially organized to be shared amongst payers. However, this becomes an issue for conditions where only mid- to long-term outcomes are clinically meaningful and relevant for the patient. In these cases, interim measures are often considered, but these interim outcomes must also be measurable and clinically meaningful. Another issue brought up was the lack of transparency in reporting clinical data, which can lead to a lack of trust between stakeholders.

Payers would like to see a distinct shift in the financial risks associated with new products toward the manufacturer, particularly when the endpoints, milestones, or length of time to continue measurement are not clearly defined. Additionally, manufacturers or a third-party contractor could provide administrative and analytical support to payers to facilitate execution and management of the performance-based contract.

If standardized frameworks are to be created for certain conditions or therapeutic areas, they must be anchored in science and allow for flexibility and outcome measure modifications if needed.

The group suggested several ideas to increase transparency and trust among the stakeholders. First and foremost, clinically meaningful and easily measurable ex-ante outcomes should be defined. To address the lack of national or international standards, a global policy provision or guideline on best practices, outcomes, and design of performance-based managed entry agreements would be beneficial. It was also suggested that a shared database of success stories should be created to enhance dialogue and information sharing, increase transparency, and set standards for outcome measurement and reporting. Most importantly, the groups noted that patient perspectives should be integrated into defining and identifying meaningful outcomes.

Results From the Groups Discussing Actual or Perceived Best Practices

The most important best practice identified for successful examples was the development of trust between manufacturers, patients, and payers. During all stages of the process of initiating and managing performance-based managed entry agreements there should be open dialogue between the stakeholders, especially with patients. It was felt that successful agreements are those that focus on the needs of patients. When patients are included in the development of the agreement, meaningful outcomes and key decision points can be better incorporated into it.

Additional best practices for performance-based managed entry agreements were identified. They should clearly outline outcome measures, data uncertainty, cost containment, real-world evidence collection and evaluation processes, and the process for performance adjudication. Dedicated data analytics expertise must be provided. The groups felt that if standardized frameworks are to be created for certain conditions or therapeutic areas, they must be anchored in science and allow for flexibility and outcome measure modifications if needed. In addition to having a nonrespondent refund or rebate, participants suggested that well-designed performance-based managed entry agreements also include explicit progress monitoring and a clearly outlined exit criteria.

How Can ISPOR help?

ISPOR continuously works on creating guidelines and tools to help improve decision making and to bridge gaps between stakeholders. ISPOR provides many training opportunities through workshops, short courses, and webinars, and with the help of the participants of this payer summit, several areas were identified for consideration by ISPOR:

- 1. Convene stakeholder groups to build trust via identifying feasible and meaningful outcome metrics for various conditions.** The main barriers recognized during the summit were those involving the level of uncertainty and the lack of trust. Therefore, ISPOR could help facilitate multistakeholder working groups or task forces to develop guidelines, templates, and methodologies and to centralize and standardize outcomes for various therapeutic areas.
- 2. Leverage the ISPOR Patient Council to transparently get ahead of the technology curve in advance of the next waves of innovation.** Working with patient groups and existing horizon-scanning organizations/networks, ISPOR could help identify and communicate promising therapeutic areas potentially amenable to performance-based managed entry agreements. The patient groups could also be engaged with other stakeholders to support data collection, identify outcomes of importance to patients, and participate in guideline development.
- 3. Develop a list of barriers and opportunities and update best practice guidance documents to reflect the current state of performance-based managed entry agreements.** ISPOR has previously created multiple best practice guidelines that are widely used within the drug development and reimbursement arenas—these should be updated regularly to reflect the current barriers and opportunities. Compiling a list of barriers and opportunities identified during this payer summit would also be invaluable moving forward.

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We would like to thank Ilze Abersone, BS, MS, Research Consultant, Vital Statistics Consulting, Hoboken, NJ, USA and Fabiana LoPiccolo-Stewart, Associate, Scientific & Health Policy Initiatives Department, ISPOR, Lawrenceville, NJ, USA for their support on the development of this article.

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RESEARCH ROUNDUP

Section Editor: **Aakash Bipin Gandhi, BPharm, PhD**, Research Scientist, RWE, Sanofi, Cambridge, MA, USA

How can health economics be used in the design and analysis of adaptive clinical trials? A qualitative analysis.

Flight L, Julious S, Brennan A, Todd S, Hind D. *Trials*. 2020;21(1): 1-12.

Summary

The article by Flight et al discusses the incorporation of health economics within the design and analytical framework of adaptive clinical trials to increase their efficiency. As opposed to traditional trials, an adaptive design relies on active data monitoring to help inform real-time modifications during the progress of the trial, which may maximize time and cost savings. While adaptive trials commonly focus on clinical effectiveness measures, the incorporation of health economics within its framework has been rarely discussed. The present study aimed to collect stakeholder opinions and views related to the use of health economics in adaptive clinical trials. The stakeholders included general members of the public (irrespective of their patient status, utilization of the healthcare system, or involvement in clinical trials), researchers, and healthcare decision makers that were involved in healthcare technology assessments. All the stakeholders answered a survey and expressed ethical, methodological, and practical considerations related to the inclusion of health economics in adaptive trials.

Relevance

Certain key thematic results emerged from the stakeholder survey. First, participants were in strong agreement that clinical effectiveness continues to be the primary component of adaptive trials despite the importance of economic outcomes to healthcare decision makers. Second, participants expressed apprehension related to familiarity with health economic methodologies. Hence, it was suggested that individuals with specialist knowledge in this area serve on adaptive trial committees. Third, participants suggested that there should be greater cohesion between health economists and statisticians on trial committees to ensure that trial methodologies and analytics result in valid and robust outcomes. In summary, while the adoption of health economic methodologies can widen the perspective of adaptive trials, stakeholder opinion (eg, not compromising the importance of clinical effectiveness) and provision of adequate training in this field must be carefully considered before the implementation of these approaches.

Precision health economics and outcomes research to support precision medicine: big data meets patient heterogeneity on the road to value.

Chen Y, Guzauskas GF, Gu C, et al. *J Pers Med*. 2016;6(4):20.

Summary

In this article, Chen et al discuss the role that precision health economics and outcomes research (HEOR) plays in helping quantify the impact of patient and disease heterogeneity on economic outcomes. Further, the article stresses the important role that big data plays in supporting precision HEOR approaches. The authors discuss the possibility of precision

HEOR replacing traditional HEOR approaches as personalized medicine continues to evolve. This can aid the development of targeted disease management approaches tailored to patient needs coupled with an efficient allocation of healthcare resources for greater societal benefit.

Relevance

Precision HEOR can offer several benefits. First, it can help pharmaceutical and device manufacturers develop market access strategies that target patient populations with relevant interventions. Second, it can help improve payer reimbursement decision making and healthcare resource allocation by accounting for heterogeneity in patient and disease-related characteristics. Third, precision HEOR can demonstrate the value of orphan drugs. For example, while drug approval for a rare disease may not substantially benefit the total patient population, precision HEOR is able to demonstrate its value for specific subgroups of individuals most affected by the condition.

Current and future use of HEOR data in healthcare decision making in the United States and in emerging markets.

Holtorf AP, Brixner D, Bellows B, Keskinaslan A, Dye J, Oderda G. *Am Health Drug Benefits*. 2012;5(7):428.

Summary

The objective of the study by Holtorf et al was to evaluate the use of HEOR data by managed care organizations in the United States for access and reimbursement decision making. The study surveyed 72 decision makers from managed care organizations and 30 Pharmacy and Therapeutic members on their views about the current use of HEOR data, associated barriers and limitations, and vision for future use. In addition to the United States, an international perspective was obtained by modifying the survey as per feedback received at a HEOR conference in Europe. Further, a pilot version of the survey was also shared with relevant stakeholders in Asia, Latin America, Middle East, and Africa. A large proportion of respondents from the United States (74%-77%) stated that HEOR methodologies were currently incorporated into their decision-making process. However, a large proportion of US respondents (66%) also revealed that quality assessments related to these methodologies were limited. Overall, a majority of the US respondents expected the use of HEOR for healthcare decision making to continue increasing in the future. The use of HEOR varied across Asia, Latin America, Middle East, and Africa regions.

Relevance

The study provides a significant benchmark for the use of HEOR in the United States that can be used for future comparisons. The study also highlighted that the use of HEOR in reimbursement and healthcare decision making continues to increase, especially in the United States.

Note from the Section Editor: Views, thoughts, and opinions expressed in this section are my own and not those of any organization, committee, group, or individual that I am affiliated with.

Virtual ISPOR Conferences and Events

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Washington, DC, USA area and Virtual Conference



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A sample of session highlights:

Plenary | Monday, May 16 | 8:30AM EDT
[HTA on the Run](#)

Plenary | Tuesday, May 17 | 8:30AM EDT
[Can Big Data Analytics Deliver on the Promises of Personalized Medicine for All? Unpacking the Health Equity Considerations](#)

Plenary | Wednesday, May 18 | 11:30AM EDT
[The Patient \(Finally\) at the Center: How Can We Leverage Digital Data to Make Patient-Focused Adoption, Reimbursement, and Management Decisions?](#)

Spotlight

Signal Session | Monday, May 16 | 10:15AM EDT
[New Analytical Approaches to 21st Century Challenges](#)

Tuesday, May 17 | 10:15AM EDT
[Emerging Methods in Real-World Analyses Involving Social Determinants of Health](#)

Continued on following page

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- 3 Peruse the latest methods, economic analyses, and HEOR news in [ISPOR's Portfolio of Publications](#). Not just a good way to keep informed, ISPOR publications offer great opportunities to get involved—both as a potential author and peer reviewer.
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ISPOR 2022 | Washington, DC, USA area and Virtual Conference continued

HEOR Theater

Monday, May 16 | 12:45PM EDT

Real-World Data for Comparative-Effectiveness Research – *Sponsored by OM1*

Monday, May 16 | 3:00PM EDT

Advances in the Development and Application of Real-World Evidence: Learnings from the United States and China

Monday, May 16 | 3:45PM EDT

Utilizing RWE and HEOR Throughout the Product Lifecycle: From Product Positioning to Market Access and Reimbursement – *Sponsored by Lumen Value & Access*

Tuesday, May 17 | 12:45PM EDT

Comparing Registry and Electronic Health Record Data for Real-World Evidence Generation: Heart Failure as a Case Study – *Sponsored by Veradigm*

Tuesday, May 17 | 3:45PM EDT

Transforming Real-World Data Into Insights That Drive Value – *Sponsored by Evidera | PPD*

Please note: As a Society committed to improving health and as a global event producer, ISPOR continues to closely monitor news and reports of coronavirus disease (COVID-19) outbreaks globally. For more about health and safety at ISPOR conferences, please visit our [Health & Safety](#) page.



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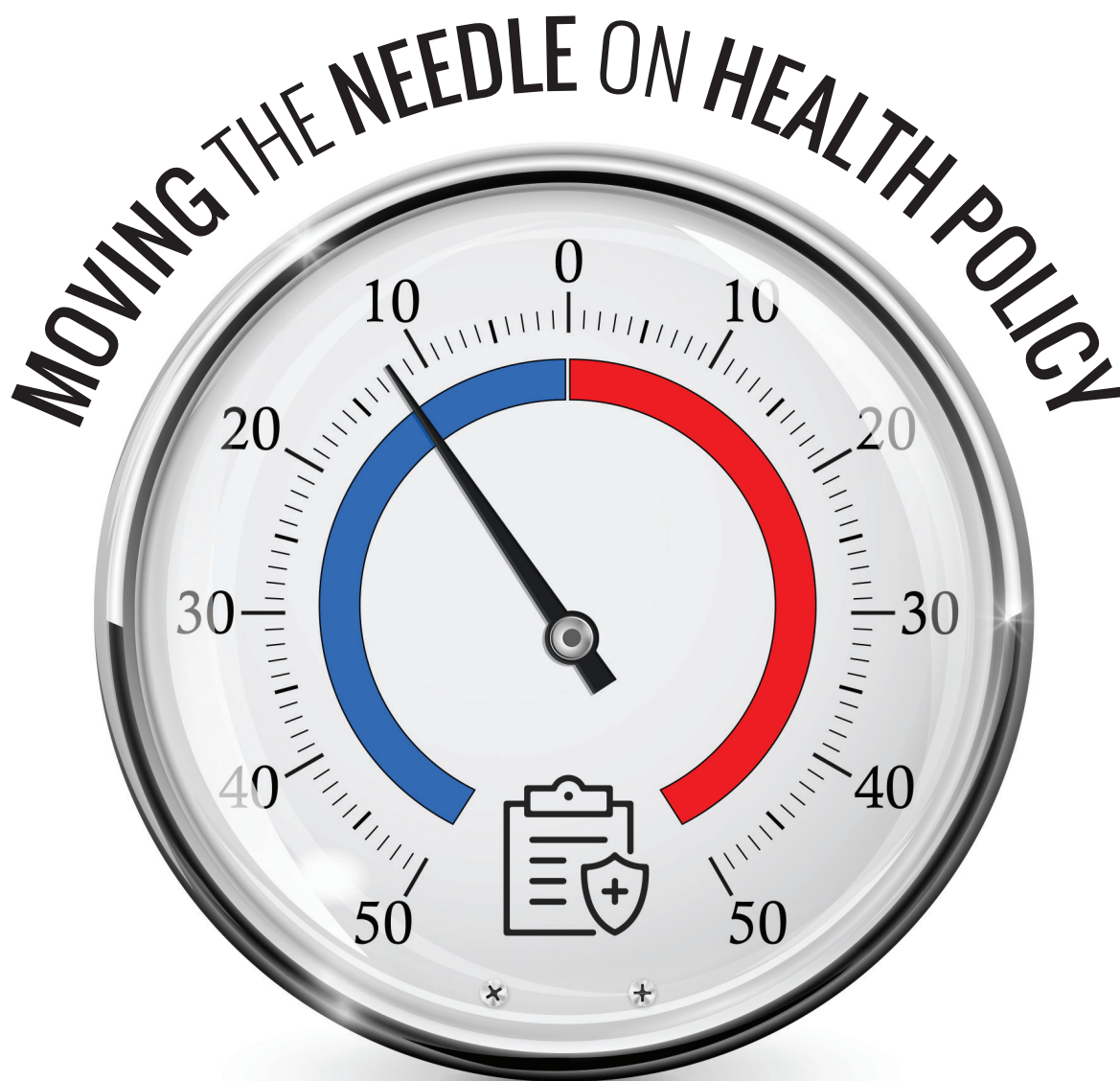
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FOCUS ON OUTCOMES-BASED CARE

The healthcare system paradigm has slowly been shifting towards real-world outcomes-centered care, and rightfully so—in 2019, it was estimated that overtreatment, low-value care, and failure to price medical services and products in the United States alone cost anywhere between \$306-\$342 billion.¹

Wasteful spending, however, is not unique to the United States and is a common occurrence across the world in high-, middle-, and low-income countries alike. It bears not only financial but also clinical burden when a treatment provided to the patients doesn't yield the expected results.



The constantly increasing demand for healthcare resources and emergence of innovative therapies that enter the market at incredibly high price points challenge traditional policymaking and reimbursement processes. This forces decision makers to reassess ways in which these resources are distributed. Using traditional clinical trial safety, efficacy, and quality of care data alone to drive healthcare decisions is no longer seen as best practice and reimbursement agencies around the world are looking for ways to complement them with population-specific insights on treatment effectiveness using real-world outcomes data.

From Plan to Action

Both clinical and nonclinical patient outcomes should be at the forefront of every treatment-related decision. In the United States and other high-income countries, most pharmaceutical manufacturers invest heavily in health economics and outcomes research (HEOR) studies to support their product by providing clinical, humanistic, and economic real-world data that they collect throughout the lifecycle of the product.² Additionally, countries such as the United Kingdom, Spain, South Korea, and Thailand have a formal way of requesting HEOR information during the health technology assessment (HTA) process allowing them to consider comparative cost-effectiveness and health outcomes data when creating health policies.

“In the Philippines, emphasis should be put on the research to have more data available, but it is mostly a budgetary issue and doing HEOR research is not a priority.”

— Chris Muñoz

However, in other parts of the world, it is not always as straight-forward. As Don Husereau, MS, Adjunct Professor, University of Ottawa, School of Epidemiology and Public Health, Ottawa, Canada, points out, “administrative data is collected differently according to how health systems are structured and without any consistent data standard,” and emphasizes that despite the efforts of making consistent decisions, there are various challenges related to mechanisms to use real-world evidence, particularly in disease areas with low patient-population prevalence. For example, Chris Muñoz, Board Vice President, Philippine Alliance of Patient Organizations (PAPO), Manila, The Philippines, explains that the HTA council within the Philippines Department of Health was created only 2 years ago and this year, patients will finally be able to submit their first topic nominations (referrals of

topics for technology appraisals that can then be used for dissemination and health policy decision making.)³ “Generally, everyone, including pharmaceutical companies and the government, can submit this form,” explains Muñoz, “but the patient form is very different—it mostly focuses on patient wellbeing after receiving the treatment, because we added a quality-of-life survey as an attachment to this form.” He adds that PAPO’s goal is to not only show the direct effect of treatment on the disease outcome, but to also provide the government with information about the effect it has on patients’ families and their everyday lives. Similarly, in most Latin American countries using health outcomes and cost-effectiveness data to support health policy decisions is not always a common practice. Eva Maria Ruiz de Castilla, PhD, Regional Director for Latin America in the Global Alliance for Patient Access (GAFPA), confirms that while some policy-related decisions in countries such as Brazil and Colombia can be driven by HEOR data, it often comes from other countries that don’t necessarily have equivalent infrastructure. Ruiz de Castilla adds that “It’s complicated—some countries are implementing HTA systems and establishing HTA institutes. They are trying to collect outcomes data, but I don’t see them use this data to decide on policies. This is more political

“We have to make institutions stronger. They need to have a framework and improve their capacity to build data tools, collect data, and collect outcomes that we need.”

— Eva Maria Ruiz de Castilla, PhD

than evidence based.” And of course, these are not the only examples. Many middle- and low-income countries are still in the process of either establishing their HTA bodies, developing region-specific frameworks or working on officially incorporating cost-effectiveness and patient outcomes data into the policy decision-making process.

Barriers Are Hard to Break Down

Muñoz points out that in the Philippines, funding is a major barrier to obtaining real-world outcomes data. “In the Philippines, emphasis should be put on the research to have more data available, but it is mostly a budgetary issue and doing HEOR research is not a priority. Studies here are financed by the Department of Science and Technology and before funding HEOR studies they would still have to fund the creation of clinical and practical guidelines. If these guidelines are not available, the program will not proceed.” He also adds that a constrained healthcare budget makes it difficult to justify long-term outcomes studies and cost-effectiveness data collection for therapeutics that soon might have more effective alternatives entering the marketplace.

“Payers often have similar background training. As a result, these payers may be less familiar with advanced epidemiological and data science methods such as real-world evidence.”

— Don Husereau, MS

The Philippines, of course, is not alone in this situation. In fact, during the 2022 ISPOR HTA Roundtable in Middle East and Africa region most participants agreed that while varying levels of progress have been made towards creating a structure and guidelines for implementing HTA assessments and real-world evidence data gathering into the health policy decision making, budget remains a significant barrier.

Lack of transparency and subsequently, trust is another obstacle holding back progress. Ruiz de Castilla explained that political instability can often hinder any advances. She explains that “We have to make institutions stronger. They need to have a framework and improve their capacity to build data tools, collect data, and collect outcomes that we need.” Ruiz de Castilla adds that if the institutions are not regulated there is always lack of trust, clarity, and as a result ineffective implementation of policies.

Despite the existing difficulties, it is apparent that HEOR data collection and HTAs are seen as invaluable tools and are gaining traction among decision makers. Husereau explains that from the Canadian observations, “Payers often have similar background training. As a result, these payers may be less familiar with advanced epidemiological and data science methods such as real-world evidence,” which aligns with the low- and middle-country expert observations that lack of

professionals and access to training is frequently one of the major barriers to real-world data implementation. Husereau adds that 1 requirement to motivate stakeholders to push for outcomes-related data inclusion in health policy decision making includes, “requiring stakeholders to have an increased trust in new methods—to work with trusted experts who have better education and awareness. This can help stakeholders be more trustful of unfamiliar approaches.”

While competing priorities among various stakeholders impede the progress of implementing HEOR data in traditional health policy decision making, both Ruiz de Castilla and Muñoz agree that focusing on patient experience is paramount and they expect to see more public involvement in decision making in the future through patient advocacy groups. However, the work doesn't stop at the data collection level. Even though equivalents to such programs as Surveillance, Epidemiology, and End Results Program exist in many countries, making the economic and patient outcomes assessments available in theory, there is no policy that requires to take them into account when making reimbursement and access-related decisions.

ISPOR Helps to Build HEOR Capacity

ISPOR has recognized the need for HEOR-related education and support and has created an HTA Council that works towards improving cost-effectiveness and outcomes research education access all over the world. It provides regional platforms for trainings, guidance, annual roundtables, and recommendations for countries interested in advancing their health policy decision-making capacity. With such collaborative effort, ISPOR hopes to provide a widely available platform for global knowledge sharing among various stakeholders.

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About the Author

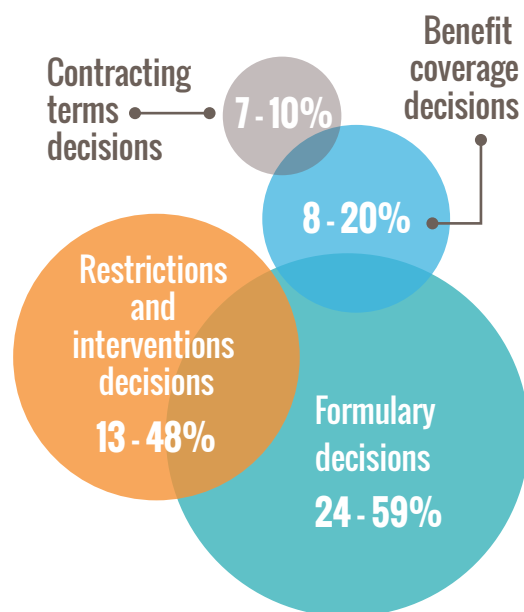
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By the Numbers: Moving the Needle on Health Policy

Section Editor: **The ISPOR Student Network**

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Influence of HEOR for decision making*



How HEOR has influenced change



Value based

Value-based healthcare evaluation (including value-based insurance design and pricing)



Learning healthcare systems

Improving health service delivery



Patient centered

Placing patients at the center of healthcare decisions



Reimbursement policy

Establishing collaborative and efficient reimbursement structures



Pricing policy

Drug pricing and decision-making schemes

5 recommendations for policy makers to translate patient-centered care and outcomes evidence to policy

Quality metrics

Include patient-centered care and patient-relevant outcomes as a dimension to measure quality of services

Objective measures

Focus patient-centered care and outcomes beyond patient satisfaction

Transparency

Make patient care experience publicly available to improve transparency of policy implementation

Funding incentive

Require healthcare funding models to incorporate performance-based payments based on patient relevant care outcomes

National indicators

Develop national indicators for patient-centered care and relevant outcomes to ensure standards across healthcare settings and institutions

* HEOR indicates health economics and outcomes research. Based on the following categories: Asthma/chronic obstructive pulmonary disease, breast cancer, cardiovascular, diabetes, gastrointestinal/colorectal cancer, hematological cancer, hepatitis C, and multiple sclerosis.

Understanding Value: The Patients' Perspectives

Editor's note: This is part 4 of a series exploring what value means to the stakeholders in healthcare. Part 1, "Expanding the Value Conversation," appeared in the May/June 2021 issue, part 2, "Understanding Value in Cancer Care," appeared in the July/August 2021 issue, and part 3, "Understanding Value: The Providers' Perspective," appeared in the November/December 2021 issue.



About the Author

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"Patients have been the one missing player in system-level healthcare decision making for most of the modern healthcare system," said Suzanne Schrandt, JD, Founder, CEO, and Chief Patient Advocate of ExPPect, Arlington, VA, USA and Chairperson for the ISPOR Patient Council.¹ Fortunately, that is changing. Patients' voices are being heard and their input actively sought when assessing value to a population. But the value of an intervention to a specific patient must be viewed in the context of that person's life circumstances, goals, and preferences—a unique lived experience.

Population-based studies can identify issues common to most patients. Questions such as, "What limitations to your daily activities does your condition cause?" usually elicit similar answers from people with the same disease. Patient advocates raise these issues in policy and research prioritization discussions. This article relates the individual experiences of 2 patients with common diseases and case vignettes from a rare disease population with a gene therapy treatment option. These stories illustrate both common themes and the importance of listening to individual patients.

Migraine

Migraine affects approximately 15% of the population. Headaches are most severe among working adults aged 18-64,² often occurring suddenly while the individual is at work. This affects productivity, relationships, and quality of life. People with chronic headaches must learn to cope with them and function in a society that expects dependability. Few people die as a direct result of headaches, but the life impact is often underappreciated. Frequent headaches disrupt daily life and create a burden for family members, coworkers, and others that must take care of the incapacitated person's responsibilities.

Ellen* has lived with migraine for much of her adult life. "My first really severe headache came at age 25," she remembers. "It was my first year in graduate school and I had a class each week with the department chairman. We had to read many papers and we never knew which of the 5 grad students he would call on to explain the paper. These 'let-down' headaches would occur Thursday afternoons and last until the next day. I slept in a bed with the lights out in severe pain with bad nausea and vomiting. Ibuprofen gave minimal relief, but it wasn't until the early 90's that I found dependable relief with an Imitrex (sumatriptan) injection. Both the injectable and the tablets caused side effects, but the side effects were nothing compared to the relief and the ability to do what needed to be done that day.

"I remember looking at my leg for about 5 minutes because the injection hurt. Can I do this? I need to do this! After the first few minutes of injection pain and trippy side effects, the pain

would dissolve and float away pretty fast." Over the next few years, other similar drugs appeared. "I tried all of them at one time or another," Ellen says, "and settled on Maxalt (rizatriptan benzoate) for efficacy and fewer side effects."

Ellen adds, "Before triptans, it was bedrest for bad headaches, so there was work and school lost time and many missed dinners or other events." For a number of years, she didn't have a primary care doctor. "After I lived through a headache, it wasn't forefront on my mind. Pain is forgettable, even severe pain, when it doesn't kill. No one talked about severe headaches back then. I had to get back to work.

Patients' voices are being heard and their input actively sought when assessing value to a population. But the value of an intervention to a specific patient must be viewed in the context of that person's life circumstances, goals, and preferences—a unique lived experience.

"Two of my worst broke through the triptan tablets, probably because I took them too late," she continued. "Both had me on the bathroom floor for hours; one at a friend's dinner party and the other on Christmas Eve at my sister's party. I don't think I ever got sympathy that was meaningful. People can feel sorry for you, but it doesn't help quality of life and who cares about sympathy when you are vomiting your guts out? It doesn't help right at the time."

Ellen reflected on the life impact of chronic headaches. "Probably my life would not have been hugely different because I am driven and am an overachiever. I work through pain unless I'm vomiting, then I get it over with and go back to work. That's common for severe headache people. Life may have been easier without the worry of having a major headache and missing out on social events. I didn't go to places that could trigger headaches. If it was a longer-haul flight for work, I had to account for that if I planned a presentation and had to come in a lot earlier if it involved travel. I avoided social events with heat, noise, alcohol, lots of people. I would never go to a New Year's Eve party, for example."

People with headaches need understanding from coworkers, family, and friends. If their migraines are frequent and not well controlled, they can't function. That includes being interested in their kids' days, cooking, driving a carpool, and being nice to their spouse. With frequent near daily headaches, frustration,

anger, guilt, and anxiety can add to the suffering. It can break up a marriage. When people give up or use headaches as an excuse to not be there, contribute, or be in a good mood, when they give in to self-pity, they start believing it's their life forever. It destroys relationships and leaves sufferers in their own misery. For some people, triptans and other newer drugs have been a game changer, but others continue to have their lives disrupted.

Diabetes

Type 1 diabetes affects 1.6 million adult Americans.³ Without insulin, they would die within 3 years of diagnosis⁴ but with today's technology they can have near-normal life expectancy.⁵ Small wearable devices monitor blood sugar levels and adjust insulin in real time. Chances are you know one of these patients without being aware they are diabetic. Onset in children is common, and training and motivation are essential. Diabetes affects overall health, self-image, and relationships, and the high cost of insulin causes financial burden.

Maggie* is a vibrant, energetic young adult diagnosed at age 8. She doesn't remember a time when "you didn't have to think about it. You could do whatever you want." She was diagnosed early when her mother, a pharmacist, recognized the symptoms. "My parents were very good about it," she remembers. "They said, 'This is your disease. We will do whatever you need us to, but you have to handle this.'" They requested that clinic staff talk to Maggie directly. "She is the one that needs to do it." They empowered me to handle it independently. They knew I could do the calculations."

"Teenagers have issues with parents—mine just had a more medical focus. 'Did you test your blood sugar?' as opposed to 'Did you have a good day at school?'"

Classmates were intrigued when Maggie returned to school. "Everyone thought I was very cool, so I was thinking this isn't so bad. Many people are embarrassed about becoming diabetic. I don't think I ever experienced that. I got to miss a week of school and do all these things. My parents bought me a cell phone, which I thought was the coolest thing ever!" In adolescence, she "hated being diabetic and wasn't doing everything I should have been. During your teenage angst phase, some people sneak out of the house; I just stopped testing my blood sugar regularly." There are challenges for a busy student, like the occasional acute hypoglycemic episode. "I remember being acute twice when I was taking a test," she confided. "I was so low I couldn't think, and I had to tell the teachers I couldn't take the test. They said what are you talking about? You're low? What do you mean? It was such a big deal for me to be OK that I would rather be high so I can take the test and not get that low."

"There were 2 life-changing technological advancements in my college years. With the Tandem⁶ control, you set your basal rate and connect it to your desktop, so it always knows your blood sugar. You need to tell it you're going to eat 50 grams of carbs,

but the natural dips and peaks—it completely evens those out. It can't increase your basal enough to mitigate having to bolus, but it does a good job. No random ups and downs. It pretty much levels this out.

"The other advancement was the Dexcom G4 continuous glucose monitor. It didn't hurt and was consistent enough that you could trust it. The US Food and Drug Administration didn't think so, but if you asked diabetics, we definitely did. Not having to test your blood sugar 8 times a day and having it on your phone? I'll take that!"

Maggie continued, "Where you really see the value from a day-to-day perspective is the things that make your life so much easier, like Novolog (insulin aspart) insulin will keep me from dying in 2 weeks, but the Dexcom is great because it'll keep me from dying in 40 years or tonight when my blood sugar goes low and I'm sleeping. It will like yell at me until I wake up. It's all those small day-to-day, make-your-life-a-little-easier things that have been the most valuable to me. I remember having prior authorizations denied for my Dexcom or for other medications. Someone who's not diabetic has absolutely no idea what this is like. How can they tell me I can't have them?"

Like many chronic diseases, diabetes affects relationships. "Teenagers have issues with parents—mine just had a more medical focus. 'Did you test your blood sugar?' as opposed to 'Did you have a good day at school?' It's always clear who my good friends are. If they know I'm diabetic and they've seen me be super low, they'll keep snacks just in case. It's not their responsibility, but it's so sweet when they do that. It gives me extra insight into someone's character."

Rare Diseases: Spinal Muscular Atrophy

With major advances in treatment of common chronic diseases, researchers are now focusing on less common conditions. Estimates of the number of rare diseases range as high as 8000.⁷ Gene therapies for a few of them are now or soon will be available. Per patient cost will be very high, but those that are truly life changing are likely to be high value.⁸

Spinal muscular atrophy (SMA) is the first rare disease with a US Food and Drug Administration (FDA)-approved potential cure. Zolgensma (onasemnogene abeparvovec) is a viral vector gene therapy approved in 2019. The first children to receive it in trials are still thriving after 5 years. Untreated, their life expectancy is 2 years at best. Early treatment is essential, as interviews with parents eager to share their children's stories demonstrate. Lucy received treatment 38 days after birth. She is a lively 1-year-old who crawls, climbs furniture, and can stand briefly unassisted. Her mother hopes that, "One day...we'll see adults, teenagers, and children just all-out living daily life."

Patti has given birth to 2 children with SMA. One died before gene therapy became available. Her sister, Addie, received it at age 2-1/2 months. "Stopping the progression of SMA means not watching my child decline," says Patti. "It means watching her actually have the ability to feed herself [and] propel herself in her wheelchair, which is something I never thought I'd see." Four-year-old Malachi was treated at 4 months. Like Addie, he uses a manual wheelchair.

Matteo, treated at age 27 days, is an energetic 4-year-old who has achieved all expected milestones, walks, runs, climbs stairs, and attends preschool. “We don’t need to do anything to manage Matteo’s SMA at this point,” says his mother, Nicole. “It really did change his prognosis. I think it’s important to share our story because it gives people hope. It shows people that the treatment is working.” His father sounds like a typical parent of a 4 year-old: “From the moment he wakes up until the moment he goes to sleep, he can outlast all of us!” Matteo already has far-reaching ambitions: “I want to be a chef astronaut, and cook on the moon.”

Only individual patients can say what matters most to them and surveys of patients with similar conditions will provide an aggregate overview.

Elena and Milan watched their first daughter take her last breath in 2010. Their second daughter, Evelyn, received Zolgensma at 2 months and is now 4-and-a-half years old. “The timing of this with SMA is so crucial,” Elena emphasizes, “Because as long as you wait, the more strength the kid would lose.” After Evelyn received Zolgensma, her parents waited anxiously to see the results. “When she started to lift her head when she was on her tummy—this is nothing less than a miracle for an SMA child, because I knew personally that kids with Type 1 SMA, they do not... and Evelyn did! If you look at Evelyn and you don’t know anything about her, you would never think that she had any problems. She’s so independent now. I can’t believe she grows so fast.” Milan adds, “Every week was exciting. Every day she does something that makes me laugh. Every day she’s doing something great.” Their experience with Zolgensma gave Elena and Milan the courage to have another child, a sister who is SMA-free. “We were relieved to know that even if she did have SMA, there is hope,” Milan explained.

These and other videos of SMA families can be seen at <https://www.zolgensma.com/family-videos>. Their experiences encourage hope that future gene therapies may enable children with other genetic disorders to live fairly normal lives.

Other Rare Diseases

Several gene therapies for hemophilia are pending FDA approval. These deliver the gene for a missing blood-clotting factor without which patients are prone to severe bleeding and require regular infusions of the missing factor. Some are poorly controlled and have frequent emergency department visits and hospitalizations. They can die from acute bleeding, and bleeding into joints causes permanent damage and disability. Annual treatment cost often exceeds \$1 million per patient, and patients’ financial burden is substantial. Because hemophilia is X-chromosome-linked, mothers deal with guilt feelings, knowing they are the source. Patients often have normal siblings, and parents struggle to balance time and attention among siblings. Family life can be interrupted by sudden trips to the hospital. β -thalassemia, a related blood disorder, also has a gene therapy pending FDA approval.

Patients with Duchenne muscular dystrophy gradually lose function and die as young adults. The dystrophin gene they need is too large to fit in the viral vector capsules, so a truncated form is being studied. Mindy Leffler has an adult son with Duchenne. Concerned that the standard trial endpoints (like the 6-minute walk test) do not reflect what matters to patients and parents, Mindy is developing better tools based on home videos taken by parents. Her company, [Casimir LLC](#), has a HIPAA-compliant cellphone app to transmit these videos, facilitating data collection for clinical studies. “As my son will say,” she told the Institute for Clinical and Economic Review’s public review committee, “Nobody cares about speed walking. Never wanted to speed walk. Don’t have any desire to do so, and it has nothing to do with my quality of life.”⁹

Resources to Improve Understanding

Whether the condition is common or rare, patients with chronic diseases face challenges that are often misunderstood by others. Survival, functioning in daily life, and quality of life are common concerns. The [National Health Council](#) website includes links to many responsible patient advocacy groups that provide education on their diseases.¹⁰ But to understand value to patients, there is no substitute for asking them. Only individual patients can say what matters most to them and surveys of patients with similar conditions will provide an aggregate overview. Patients with chronic disease want to be understood and health economists and policy makers need good information to assess the value of the expensive—but potentially curative—treatments being developed for rare diseases.

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Our Sickle Cell Normal: The True Cost to the Patient of Sickle Cell Disease



I sat on the floor as the nice ladies handed my parents a black garbage bag full of wrapped gifts. Once the door latched, Marqus and I bolted to the bag and impatiently waited for our mom to start reading the labels. “Girl, age 8.”

“That’s me!” I exclaimed.

Mom continued, “Boy, age 10-14.” Marqus clutched the box to his chest, a smile stretched across his face and he met me on the floor to tear off the wrapping paper. Our mom continued to read the labels on the gifts. Marqus and I chirped back, “That’s me!” when the description of “girl” or “boy” and the age matched us. Our oldest brother, who was 16 at the time, calmly waited for his smaller, more grown-up gifts from the bag.

These are the memories that come to mind as I think about my journey as a sister to a sibling with sickle cell disease (SCD). My brother, Marqus, lived to 36 years old with SCD. He passed away June 22, 2020, during the height of the COVID-19 pandemic. We remain grateful to this day that we were allowed into the hospital to sit with him.

SCD shaped our entire lives, but it always felt like the normal way to live. SCD is a hereditary blood disease that disproportionately impacts Black and Brown people living in the United States. With the diagnosis comes the weight of stigma, prejudice, discrimination, high costs, and little access to quality care. As a result, our mother learned how to navigate the US healthcare system, thus equipping her with tools she needed to seek care for Marqus. Our family was a two-income household, had commercial insurance, and sat firmly in the middle class. Yet, no matter where we hovered in society, the disease “sickle cell” engendered other terms like “Medicaid population,” “drug seekers,” “drain on the system,” “poor people,” and even the mentality that “they don’t deserve new treatments.”

In 2016, after Marqus was accused of being a drug addict during a 6-week hospitalization, he called me and said, “Something needs to change in my lifetime.” We spent the next several years building an organization, Sick Cells, to elevate the voice of the SCD community and influence decision makers. Our vision is to empower the SCD community and show that their stories are powerful. We strive to educate various stakeholders

on the spectrum of care so they understand the reality of life for someone living with SCD. We know that only 1 in 4 patients with SCD receives the standard of care.¹ According to the US Department of Health & Human Services, expenditures for patients with SCD are 6 times higher than non-SCD patients on Medicaid and 11 times higher than non-SCD patients with private insurance. It’s estimated that the United States spends \$2.98 billion per year to care for people with SCD, and they are still dying in their 20s, 30s, and 40s.² With new treatments on the market, we hoped that these statistics would change; however, as we continue to do our work, we learn that many patients experience delays in accessing new treatments as a result of utilization controls, and oftentimes the lack of a care team to prescribe the treatments.³

Marqus and I discussed these statistics during his hip replacement journey in 2018 and we decided to add up our medical expenses leading up to the procedure. The conversation began in 2017, the year we incorporated Sick Cells, when Marqus had a femoral head collapse and required a total hip replacement, 2 common complications of living with SCD. But before he could get a hip replacement, his chronic leg ulcers needed to close. To close the leg ulcers, he had to go through recurring apheresis blood exchanges; however, his port-a-cath could not tolerate the pressure of the transfusion. Every 6 weeks, Marqus went into the cath lab so an intrajugular catheter could be placed for receiving the exchange transfusion. When he got the news about his delayed hip replacement surgery and the need for frequent blood exchanges, he decided to go outside with our family dog to get air and had a fall, breaking his knee. He was too high-risk for surgery to fix the knee, so he was put on complete bed rest for a year before his hip replacement so his body could heal. Instead of budgeting just for the hip replacement, we were now budgeting for 6 conditions or procedures.

Marqus called me daily with updates. “Ashley, the pain is bad. It’s bone against bone, but if I meditate long enough, I can get through the grocery store one time. I’ve shrunk a few inches too.” Bone-on-bone pain in his hip. Open leg ulcers on both ankles. A suture in his neck from the intrajugular catheter to complete the apheresis blood exchange, the only treatment that seemed to work on closing his leg ulcers. I’d always tease him to lighten the mood, “It takes all the specialists in the land to put Humpty Marqus back together again.” Marqus had the hip replacement surgery on August 6, 2018. He was disabled and living with my parents. He also received \$720 each month from his Social Security Insurance benefit. In order to navigate the costs of seeking care, he was on both



of our parents' insurances, and they shared medical costs. In some instances of long hospitalizations or acute situations, I contributed financially to the family medical fund or would cover other household expenses, as I did in the period leading up to the hip replacement. By July of 2018, Marqus had hit his \$10,000 maximum out-of-pocket, which didn't normally happen until November.



These out-of-pocket costs were tied to not only direct medical expenses but to indirect costs of treatment. During July, Marqus had 15 doctors' appointments with specialists to clear each part of his body for surgery. Each visit cost them a copay ranging between \$38 to \$50. In July alone, they paid about \$600 in copays. Most doctors' appointments had an additional cost associated with them if any special tests, procedures, or new equipment

were necessary, which they often were. For example, Marqus saw his cardiologist prior to surgery and then had to return for a stress test to make sure his heart was healthy. The copay cost \$40 and so was the test, totaling \$80 for that visit. On top of all the appointments, Marqus still had monthly costs of medications. He took 12 different medications every day. With their insurance, he paid about \$500 a month for everything.

Other indirect costs like gas and time off from work are not typically measured when discussing value or healthcare, but they contribute substantially to monthly costs related to care. In many cases, our dad would make repeated trips to the same pharmacy because the medications were not ready when he would arrive for pickup. Our dad had to drive to 2 different pharmacies outside of Marqus's hospital, further adding costs related to transportation. Marqus's pain medications were at one pharmacy. His leg ulcer compound cream was at a small specialty pharmacy, the only pharmacy that could compound it. The medicine to treat his comorbidities were at CVS, and 2 other medicines to treat his SCD and prevent iron overload were mail order. Our parents or Uber took Marqus to all of his appointments.

Because our dad was an electrician and an hourly worker, he didn't receive paid sick leave, making any time away from work an instant financial loss. Our mom was a nurse and saved her sick leave to be present at the time of the procedure. Ultimately, they decided it was more cost-effective for our dad to accept a layoff so he could get Marqus to all the presurgery appointments and coordinate his care. In July 2018, our dad made 24 trips to doctors' appointments and around 20 trips to pharmacies.

For the major appointments, our mom stayed home from work to attend. When we totaled the hours of work our parents missed in July 2018 to prepare for this surgery, my dad lost a total of 160 hours and my mom lost 30 hours. We didn't total the money spent on eating out, groceries, the water budget

(because people with SCD have to stay extra-hydrated), or my flights back and forth to Illinois to help out at home. On average, a 2009 estimate stated that someone with sickle cell would spend \$460,000 or more over their lifetime for care.⁴ Our family can easily say that statistic is true.

But before we became advocates, or had a nonprofit, or even had the words to describe how others viewed us with this diagnosis, this was what we did. Sickle cell was our normal. Medical bills and prescription costs came first. Marqus needed it and so did the rest of us when we also got sick. Sometimes the lights or gas were turned off; our house was foreclosed 5 times in the course of my lifetime. My mom would let us use the Blue Cross Blue Shield bills as kindling for bonfires and we mapped out hospital emergency rooms before any vacation we ever took. When Marqus would go into a pain crisis at night, we would all gather in my parents' bed and rub his legs because, truthfully, pain medications are just a Band-Aid, not a disease-modifying treatment. We also lived between the crises. I rode horses. We went to Scotland on a family vacation. Marqus was manager for all the school sports teams. All 3 of us kids played music and took lessons near Marqus's children's hospital. Marqus's hospital appointments and admissions in Chicago meant 25-cent wing nights at the chicken wing spot down the street. From my perspective, we had our version of a normal life.

Marquis hopes that the next generation of families living with SCD will not have to suffer so much. He hopes that future patients will have medication to treat their SCD and can have access to high-quality care, access to providers who are educated about their condition, access to robust coverage for treatments and therapies, they can live long lives.



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Principles to Support Access to Multi-Indication Oncology Combinations

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Data show that oncology combinations are less available and take longer to get reimbursed than monotherapies across a range of countries

Three principles are proposed to support access to oncology multi-indication combinations: (1) assessment as a single entity versus standard of care; (2) confidential combination-specific rebates; and (3) tracking use of combinations to enable said rebates

Introduction

Combinations of new innovative oncology therapies increasingly represent the preferred treatment option for many patients, delivering significant benefits and prolonged survival compared to monotherapies. However, access to branded combinations poses several challenges, particularly where the constituents are produced by different manufacturers and the medicines have multiple indications.

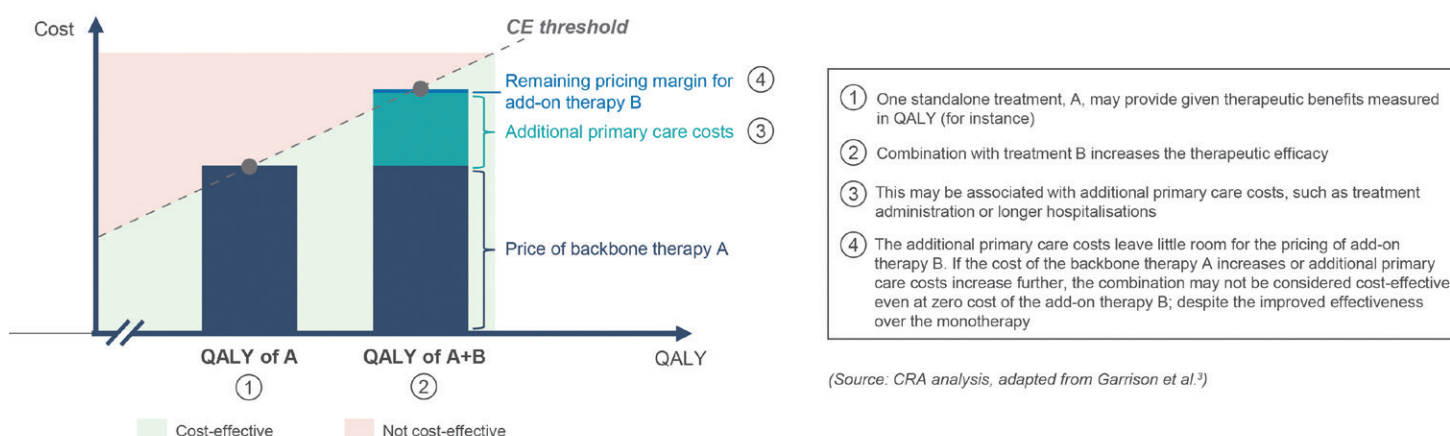
Advances in Treatment

While combination therapies are already used in oncology (such as combinations of chemotherapy treatments), in recent years there have been significant advances in treatment with the introduction of targeted therapies and immunotherapies. Just a few years ago, combination therapies had little effect on progression-free survival and overall survival, now they are beginning to show significantly positive effects; every combination therapy denied to patients could have serious consequences on their health outcomes. Combinations of these new innovative oncology therapies increasingly represent the preferred treatment option for many patients, delivering significant benefits and prolonged survival compared to monotherapies. However, access to branded combinations poses several challenges, particularly where the

constituents are produced by different manufacturers and the medicines have multiple indications. These difficulties ultimately lead to the “combination challenge”: although a combination would deliver benefits to patients and the healthcare system, and the medicines could be priced in a manner that rewards the companies involved and would represent good value for money for payers, the rigidities in the pricing and reimbursement system prevent patients from gaining access to new, innovative combination medicines. The application of rigid cost-effectiveness can be even more problematic, potentially leading to a phenomenon where a combination may not be cost-effective even when the add-on therapy is priced at zero cost (Figure 1).

During a symposium at the Global ISPOR conference on May 18, 2021, the challenges associated with providing access to oncology combinations, particularly where each constituent is produced by different manufacturers and is present in multiple indications, and the potential approaches to address these challenges were discussed. Tim Wilsdon, Vice President, Charles River Associates, presented a new study that investigated the level of access to combinations in the market today, the challenges affecting branded combination therapies in oncology, and the potential

Figure 1. Additional costs arising from longer duration of treatment may mean that there is no possibility of cost-effectiveness for a combination treatment, even if the add-on is priced at zero.



CE indicates cost-effectiveness; QALY, quality-adjusted life year.

policy solutions. He noted that despite the benefits of combination products (for example, addressing drug resistance and targeting specific patient population subsets), there are challenges to recognizing the value of combinations, especially when constituents may be owned by different manufacturers and may be applicable in multiple indications.

The Challenges Presented by Combination Therapies

To document the impact of the challenges, Charles River Associates performed a numerical analysis. Data on all branded oncology combinations approved in the European Union between January 2015 and October 2020 were collected. The availability of and delay associated with branded oncology combinations was compared to all oncology therapies. A range of stakeholders were also interviewed to validate and support the conclusions. The study looked at the 2020 reimbursement status for each of the 14 oncology combinations approved by the European Medicines Agency during the study period. **Figure 2** shows the reimbursement status for the combinations studied—a smaller percentage of combination products were reimbursed, versus noncombination products. Furthermore, when the combination involved constituents from more than one company, a lower proportion were reimbursed compared to when both constituents in the combination were owned by a single company. In addition, the analysis suggests that countries with a cost-effectiveness threshold find it more challenging to reimburse the combination therapies. For those combinations that are recommended, the time to reimbursement is longer compared to the average time for all oncology products across the countries included in the study. **Figure 3** compares the time to reimbursement for oncology combinations and oncology monotherapies.

The qualitative component of the research suggested that the challenge to reimbursing combination therapies is a structural one. Only one of the manufacturers, the one of the new add-on therapy, is involved in negotiations with price and reimbursement

authorities regarding the price. It may not be possible for the manufacturer of the add-on therapy to charge a price that results in the combination being cost-effective, even though it offers clinical benefits to the patient. Where rigid cost-effectiveness thresholds are applied, this problem is exacerbated.

There is a range of even more complex challenges: one or more therapies may be launching in their second or more indication, with the manufacturer seeking to avoid price erosion in the

primary indication; the combination may compete with one of the constituents; if one constituent is near loss of exclusivity, its incentives for expanding into the combination may be small.

Finding a Way Around the Difficulties to Patient Access

In terms of access and usage, there are also delays to inclusion in clinical guidelines and inappropriate incentives for prescribing combination therapies. Advocates find it very frustrating when a patient cannot access a combination

Figure 2. The reimbursement status in October 2020 of branded combinations (including both multiple- and single-sponsor combinations) approved in the European Union between January 2015 and June 2020.

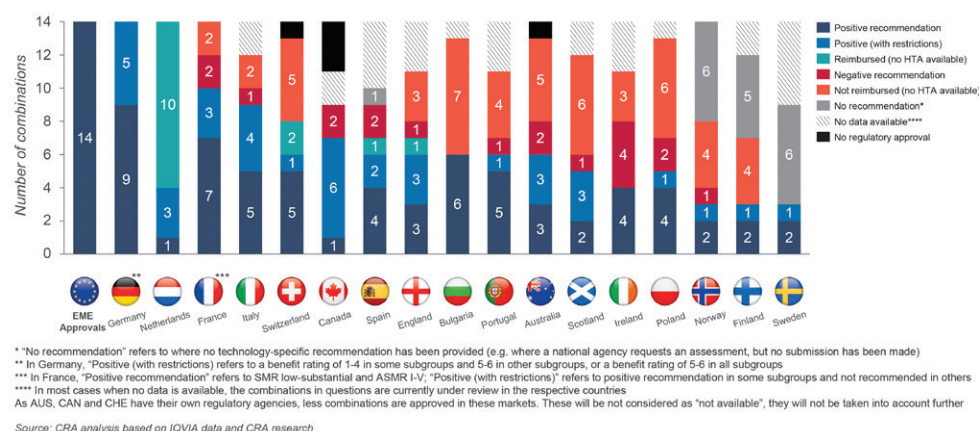


Figure 3. Median time between regulatory approval and reimbursement for the combinations (including both multiple- and single-sponsor combinations) in the study that were approved for reimbursement, compared to the same time measurement for all oncology medicines as reported in the EFPIA WAIT indicator.

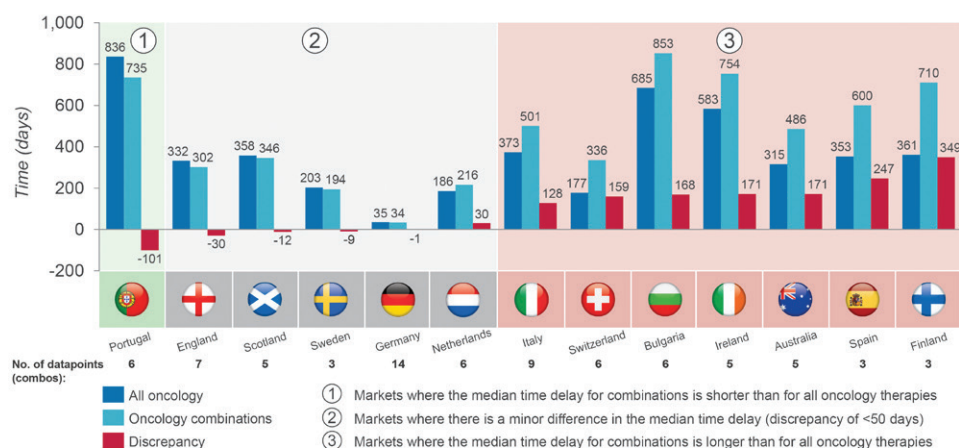
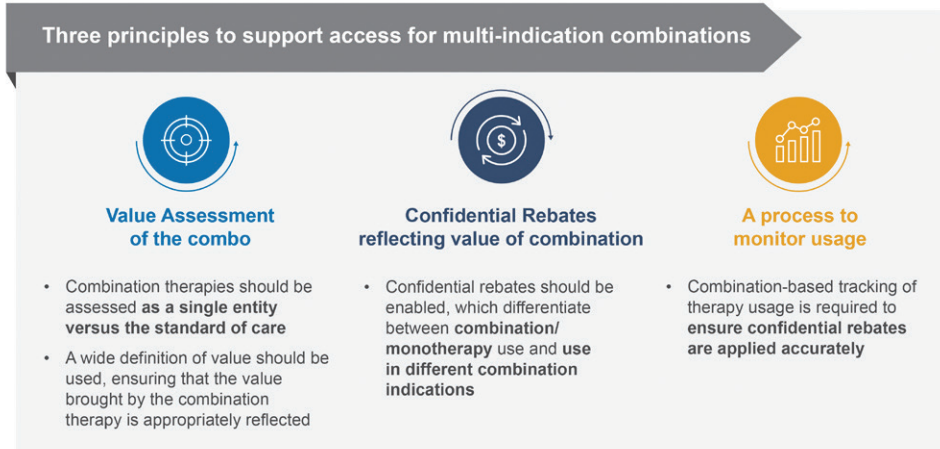


Figure 4. Three fundamental requirements to enable policy solutions are needed to solve the policy challenge.



therapy that works a lot better than the monotherapy they have access to. For example, The International Kidney Cancer Coalition is doing its best to educate patient advocates; however, there are therapies that can be cost-effective yet are not getting to patients because of this.

Three principles to support access to multi-indication combinations were proposed (Figure 4): (1) combination therapies should be assessed as a single entity versus the standard of care, including the use of a wider definition of value, ensuring that the value brought by the combination therapy is appropriately reflected; (2) indication-specific confidential rebates should be enabled, which differentiate between combination and monotherapy use and use in different combination indications; and (3) systems should be developed to track the use of medicines in combination in order to enable accurate calculation of the rebates envisaged. Although these principles can be considered universally useful, in order to address the full range of challenges, country-specific solutions will be required.

Concerns remain that many payers still appear to see the “combinations challenge” as an issue for the future rather than now. Furthermore, so

far payers and health technology assessment bodies have tended to assume this is an “industry problem,” whereas it is actually a challenging situation for everyone concerned. It is therefore desirable for all the stakeholders to be engaged in the debate and to work towards a set of solutions.

Every combination therapy denied to patients could have serious consequences on their health outcomes.

Payers should recognize that this is causing problems for patient access now and commit to working with industry and other stakeholders on solutions. The actual solution is likely to be location-dependent and needs local engagement because the influence of the law is critical and each country brings its own “remit” and “culture” regarding a solution. It must also be recognized that the challenge does not end at the reimbursement decision as there remain concerns about usage and uptake. Doctors outside of large centers do not necessarily have the same access to information about combination therapies or how to use them, and these doctors are needed to represent their patients.

Conclusion

As we are moving towards a “combinations” world in cancer treatment, we have the opportunity to achieve better outcomes for patients, turning cancer from a deadly into a manageable disease. However, empirical data show that patient access to combinations faces several hurdles. To date, access issues have been addressed on a product by product basis, but this approach is not sustainable going forward. Given the number of such products in development, these challenges will become a significant issue for patients and society. Certain policy principles could be applied to create the conditions for negotiating sustainable access, in particular an appropriate value assessment, combination-specific rebates, and the tracking of usage. To achieve better access to combinations, a dialogue around these principles between industry, patient advocates, health economists, and authorities is needed.

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Tips of the Trade: Delivering Patient-Centricity With Digital Real-World Evidence

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There are potential obstacles to engaging patients in this research, including uncertainty surrounding when and how patients should be brought into the process.

The authors describe a number of tried-and-tested approaches to involving the patient community.

Introduction

When it comes to drug discovery there is a wealth of insight to be gained from the patient community. Involving patients in the design and development of real-world evidence studies, which in turn complement traditional clinical trials by demonstrating patients' lived experience of the condition and its treatments, can be a powerful means of emphasizing patient-centricity in drug development. In this article, the authors explore the technicalities of engaging patients in real-world evidence studies.

Acknowledging Patients as Experts

Until recently, a culture has prevailed in the development of new medicines whereby research has been conducted “on,” “about,” or “for” patients.¹ In contrast, patient-focused drug development ensures that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into the development and evaluation process.² This involves a shift from relying solely on clinician expertise to assess disease burden and treatment impact to acknowledging patients as “experts by experience” and involving them alongside clinicians.³ The patient's perspective is actively sought to understand their experience of the disease and to design research around what matters most to them. For example, if a study demonstrates that a treatment generates improvement in a particular clinical metric while separately patients do not report any improvement in how they feel or function, then the value of the research is questionable. Understanding the patient perspective and involving patients early in research design can help avoid such misalignments.⁴

Real-world evidence has an important role to play in generating the patient insights needed to deliver truly patient-centric clinical programs.⁵ Real-world evidence is derived from observational data obtained outside of randomized controlled trials. Within randomized controlled trials, selection, treatment, and assessment are tightly defined and controlled to maximize internal validity. In contrast, real-world

evidence tends to select study subjects and assess outcomes much as they are, providing a more representative picture of the average patient's experience of the condition in their everyday life, and the value of treatments as they are provided in routine clinical practice.⁶

A culture has prevailed in the development of new medicines whereby research has been conducted “on,” “about,” or “for” patients.

The Patient Perspective in Real-World Evidence

Incorporating the patient perspective into the design and development of real-world evidence studies can improve the quality of data collected as well as its relevance to patients. Engaging with patient groups can also support faster, more cost-effective and representative recruitment into real-world evidence studies. However, there are potential obstacles to involving patients and patient organizations in the design and delivery of this type of research.⁷ These include:

- Uncertainty surrounding when and how patients should be brought into the process
- Resistance or friction from other stakeholders
- Challenges catering to variable levels of health literacy
- Tight timelines for projects, which may discourage investigators from setting aside the time needed to engage properly with patients
- Lack of access to patients, especially within rare diseases
- Patient concerns that researchers' requests for their involvement are not “genuine”

When the objective is to facilitate patient-centric solutions for the pharmaceutical industry, it follows that potential participants in real-world evidence

studies should have the opportunity to shape the way in which this evidence is produced, so that it is of the greatest value. With this in mind, there are means of circumventing the possible obstacles to patient engagement in order to respect and make the best use of this potential.

Case Studies in Collaborating With Patient Advocacy Groups in Real-World Evidence Studies

Digital methods are increasingly being used to conduct real-world evidence studies on behalf of the pharmaceutical industry. The case studies referenced here involve the use of bring-your-own-device technology to gather patient-reported data in real-world settings, a methodology that can be developed and implemented across different conditions. Bespoke questionnaires are combined with validated patient-reported outcome instruments and delivered to study participants on mobile devices, typically via an app, to gather data on the characteristics of the patient population, treatment patterns, burden of disease, and impact to health-related quality of life. The insights and evidence generated by these studies have been used to improve understanding of real-world populations and treatment practices, enhance clinical trial design, and support regulatory and health technology assessment submissions. Patient advocacy groups and potential participants have been important collaborators in the design, development, and delivery of these real-world evidence studies.

Overall Study Design

Face-to-face interactive onboarding workshops are held with patient advocacy groups, representatives, and patients from target countries to provide insights for the design and implementation of the study. This includes input on:

- The components of burden of disease that should be addressed
- The relevance of different custom-made survey questions and patient-reported outcomes instruments and the acceptable frequency of administration
- The potential usefulness of importing patient-generated health data into the app

- The recruitment plan
- Communication methods

In one study exploring the real-world impact of a rare, chronic neuromuscular disease, the Scientific Advisory Board included at least one patient advocacy group representative from each target country (spanning the United Kingdom, the United States, and several European countries). Patient advocacy group members of the Scientific Advisory Board were consulted during the initial conceptualization of the study to ensure that the proposed design and outcomes were relevant to patients and were involved in reviewing and providing input on key study materials, including the protocol and patient-facing elements of the smartphone app. Importantly, consulting the Scientific Advisory Board from the outset has enabled the study's adaptation to meet country-specific requirements and cultural standards.

In another study, patient representatives were consulted extensively to understand the potential burden of completing surveys and patient-reported outcomes instruments, especially the real-world practical obstacles to completion for participants. This allowed for the content and format of the surveys to be optimized, providing sufficient detail for robust and meaningful insights while ensuring that completion rates and response quality remained high.

Recruitment

Patient organizations have played an important role in recruitment and retention of study participants, by providing guidance and communicating and advocating the study with the patient community. Patient advocacy group networks have also been an important route for acquiring validated and reliable study participants.

Remote recruitment models can be particularly valuable for rare disease studies, enabling sufficient participants to be acquired from small and geographically dispersed populations in a cost-effective manner. However, in studies where participants are recruited remotely, rather than physically at clinical sites, the risk of acquiring false participants must be addressed. Participants acquired via

patient advocacy group networks are much more likely to be genuine, are self-selected as more engaged, and are usually knowledgeable about their conditions. Consequently, the likelihood of either falsified or inaccurate responses is much reduced. Self-confirmed validation of participants from patient advocacy group networks can be more effective compared with individuals recruited by other routes, where the process for validating identity and diagnosis can be challenging.

Real-world evidence has an important role to play in generating the patient insights needed to deliver truly patient-centric clinical programs.

Maintaining Engagement

Feedback can be sought from users as the studies progress in order to improve the user experience of the apps and promote ongoing engagement. Participant preference and satisfaction with the app is recorded interactively through online polls or focus groups. One advantage of digital technology is that it can be harnessed for large-scale feedback from study participants to adapt patient-reported outcomes instruments.

In a study exploring the real-world burden experienced by patients with melanoma in the United Kingdom (My Melanoma, developed in partnership with the charity [Melanoma UK](#)), the research team implemented the patient-reported outcomes version of the Common Terminology Criteria for Adverse Events ([PRO-CTCAE™](#)), a measurement system developed by the National Cancer Institute to capture symptomatic adverse events in patients on cancer trials. The initial version of the bespoke study app contained 11 items from the PRO-CTCAE instrument item bank, selected by oncologists and as a result of a literature review. To ensure that the adverse events of greatest relevance to patients were included in the app, Melanoma UK study participants with any type or stage of melanoma were invited to participate in an online survey, where they were asked to rate the relevance of each of

the 78 adverse events in the item bank. Eight of the adverse events identified by online survey respondents and further corroborated by a focus group were not included in the original study app; the version of the PRO-CTCAE implemented in the study was subsequently updated to reflect the findings. This demonstrates the importance of including patients in the design of patient-reported studies, in order to ensure that the most relevant data is captured.

Concluding Remarks

Study sponsors and investigators should recognize that patients and patient organizations can provide invaluable input into the design, development, and implementation of patient-reported real-world evidence studies. While there are potential obstacles to successful collaboration, these can usually be overcome. By engaging patients and patient advocacy groups as early as possible in the design process and seeking their input throughout the various stages of research, researchers can ensure that the studies are tailored to their target population, measure what matters, and have the support and engagement of the patient community that is needed to collect rich, consistent, and representative data over time.

Developing relationships and communicating and consulting with patients (eg, through webinars, workshops, and focus groups) requires an investment of time and resource. Securing the input and engagement of

the patient community to shape and deliver real-world evidence studies can, however, increase the quality and relevance of study outputs, and may even reduce the total time to complete a study in some circumstances, for instance by accelerating recruitment.

By engaging patients and patient advocacy groups as early as possible in the design process, researchers can ensure that the studies are tailored to their target population, measure what matters, and have the support and engagement of the patient community that is needed to collect rich, consistent, and representative data over time.

This is particularly relevant for rare diseases, where patients can be both hard to reach and the obstacles to their involvement and engagement in studies poorly understood. Should this

approach be implemented in real-world evidence studies as standard practice, collaboration with patients and patient advocacy groups could soon become the rule rather than the exception.

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Early Reflections on Stakeholder Engagement in Economic Model Development to Inform Value Assessment

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The Innovation and Value Initiative is testing a continual stakeholder engagement approach to economic model development to inform value assessments.

Early stage insights show that such an approach may result in economic models being more widely considered by different stakeholders.

In value assessments, we strive to ensure maximum benefits for resources used while identifying treatments appropriate and beneficial to individual patients. However, stakeholders may have very different perspectives of what constitutes value and how to measure it. In recent years, the health economics and outcomes research (HEOR) community has increasingly called for a more open and transparent process that engaged different stakeholders (eg, with patients) to account for such differences in methods and procedures to inform value assessments.¹⁻³ However, the “how-to” of a continual stakeholder engagement process and its impacts on value assessments remain an understudied area.

Advancing Best Practices in Value Assessments

The nonprofit Innovation and Value Initiative (IVI) is dedicated to working with different stakeholders to advance the methods and practice of value assessments. A focal area for IVI is developing flexible and rigorous economic models in specific disease areas as part of its open source value platform (OSVP), to demonstrate novel methods and best practices in value assessments that

can meet the decision needs of diverse stakeholders.

In July 2020, we launched an initiative to build its third OSVP model, focusing on major depressive disorder.⁴ As part of this initiative, we are testing a novel approach to economic model development (**Figure 1**), wherein diverse stakeholders are engaged from the outset and throughout different phases of model development (ie, model design, construction, validation, and application). We hypothesize that such an approach will lead to a more relevant and useful economic model that can generate meaningful insights for different stakeholders.

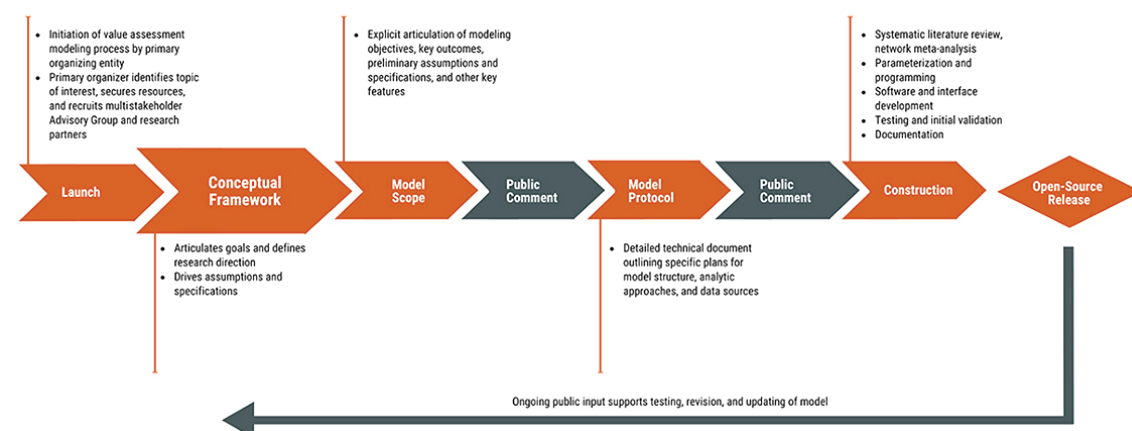
Early Stages and Insights

As a first step, we established a 20-member multistakeholder advisory group including thought leaders and experts representing patient groups ($n=5$), industry ($n=3$), researchers ($n=2$), clinicians ($n=5$), payers ($n=2$), and employers ($n=5$). (Note that certain members represented more than one perspective.)

A year after launching this effort, we worked with the advisory group to finalize the model scope document and

Figure 1. A continual stakeholder engagement approach to economic model development.

Development Process for Economic Models With Multistakeholder Input



is currently working towards finalizing the model protocol. Our early stage findings show that continual stakeholder engagement yields important insights for the model design and the outcomes that should be included in economic models to be more widely considered by different decision makers (Figure 2).⁵

This article summarizes the operational considerations and lessons learned in this ongoing process of stakeholder engagement for our OSVP model development. We share these insights to assist other researchers to implement a continual stakeholder engagement approach, and to increase the body of work that demonstrates the importance of engagement in development and application of new methods to inform value assessments (Figure 3).

Launching the Stakeholder Group

IVI's premise at the outset was that the OSVP model development should be informed by stakeholder guidance. Therefore, our first task was to establish a multistakeholder advisory group representing diverse perspectives. Before reaching out to stakeholders, we took the important step to clearly define the roles and responsibilities of the advisory group and the expected level of engagement. In our initiative, the role of the advisory group was to provide perspectives and insights that inform and validate assumptions and technical choices. We also specified the

approximate duration and frequency of engagement over the course of model development. These details were described in a brief overview document shared with the potential participants during outreach.

Identifying the individuals with the relevant expertise, interest, and availability to participate in such an effort is perhaps the most challenging aspect of launching this type of initiative. We reached out to IVI's advisory boards, membership network, and research partners to seek suggestions on potential candidates. To ensure that we heard from a broader community of stakeholders, we made a deliberate effort to identify candidates that were not in our immediate connection circles. We then shared the brief overview document with these candidates and met via teleconference to discuss the project. For those who were not able to participate, we asked for recommendations and referrals.

Facilitating Continual Engagement Prioritizing Questions for Discussions

Throughout engagement, we have found it important to prioritize the questions and tailor the process for feedback elicitation based on the expertise of the participants and type of communication channel (eg, group discussions). In the early stages, we held monthly full-group meetings (of 90-minute duration). In such meetings,

we found that we were able to address 2-3 discussion topics per meeting at most. Broader and conceptual questions (eg, patient factors missing from the current value assessments in major depressive disorder) are more suited for full-group discussions, especially during the initial conceptualization phase (eg, key modeling objectives) of model development, while more specific technical questions (eg, statistical techniques to extrapolate long-term efficacy rates) require small-group discussions with experts with relevant experiences.

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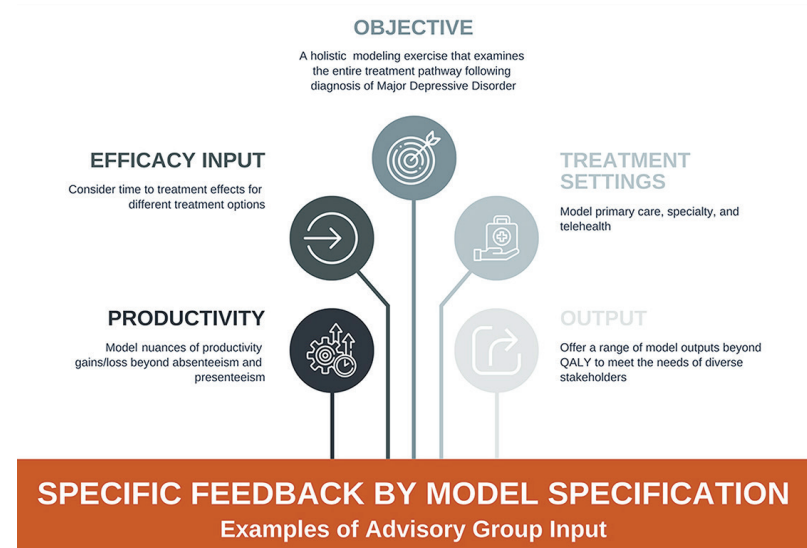
Utilize Multiple Communication Channels

We have used a variety of communication channels to elicit feedback, including email updates, surveys, small- and large-group discussions, and individual conversations. We have found that it is important to tailor the communication approach based on the questions, areas of expertise of the stakeholders, and individual preferences for providing input. In full-group discussions, we prepare prereads to provide advisory group members with uniform and sufficient background and prepare specific questions to elicit high-quality feedback. Since this is an ongoing learning process, we have worked to adapt based on feedback from stakeholders and to customize communication approaches. For example, we are currently exploring developing video clips to better illustrate key questions.

Respect Participants' Time

Time, or the lack thereof, is a major challenge. We have attempted to avoid over-burdening the advisory group with meetings and lengthy document reviews, but also keeping them informed of our project. On average, we keep the monthly time commitment to be

Figure 2. Examples of advisory group input informing model development.



QALY indicates quality-adjusted life year.

less than 2 hours. Communications channels can be tailored to facilitate input collection, and researchers should adhere to the delineated roles and responsibilities of the advisory group specified at the launch of the group. We have opted to acknowledge stakeholders' time and contributions by providing an honorarium to all participants. If a project has a limited budget, it is especially important to compensate people with the condition of interest providing patient-specific information.

Work To Ensure Transparency

To build trust and foster an open environment for learning and discussion, research teams should take steps to ensure transparency throughout the process. In our effort, we have documented all discussions and feedback, and created a shared online folder where participants can easily access all materials. For the major depressive disorder advisory group, we communicated from the outset that: (1) the role of the advisory group is to advise rather than to vote on decisions, (2) the meetings should be viewed as brainstorming sessions, and (3) we might not be able to consider all recommendations in the initial version

of the model. As a result, the advisory group felt comfortable in brainstorming as a group. Participants are free to use information from discussions in an anonymized format. Following feedback elicitation, we synthesized learnings and shared with the advisory group how their insights informed the model design. In prioritizing responses based on feedback, we also provided clear explanations to the advisory group of the rationale for our decisions (more on this below).

Lessons From Stakeholder Engagement

"Translations" Are Sometimes Needed

In aggregating feedback, researchers might need to translate both qualitative input into quantitative input for modeling purposes, and technical details for a less technical audience. On occasion, this required additional literature searches and follow-up discussions with specific stakeholders. For example, a key concept proposed by an advisory group member was "career disruption," where an individual with Major depressive disorder might not achieve full career potential over a lifetime. To translate this in the modeling context, we engaged with several members in

small-group discussions to understand ways to measure "career potential" and conducted literature searches to identify existing estimates of such influences.

Stakeholder engagement has the potential to improve the value assessment methods and lead to economic models more useful and relevant to different stakeholders.

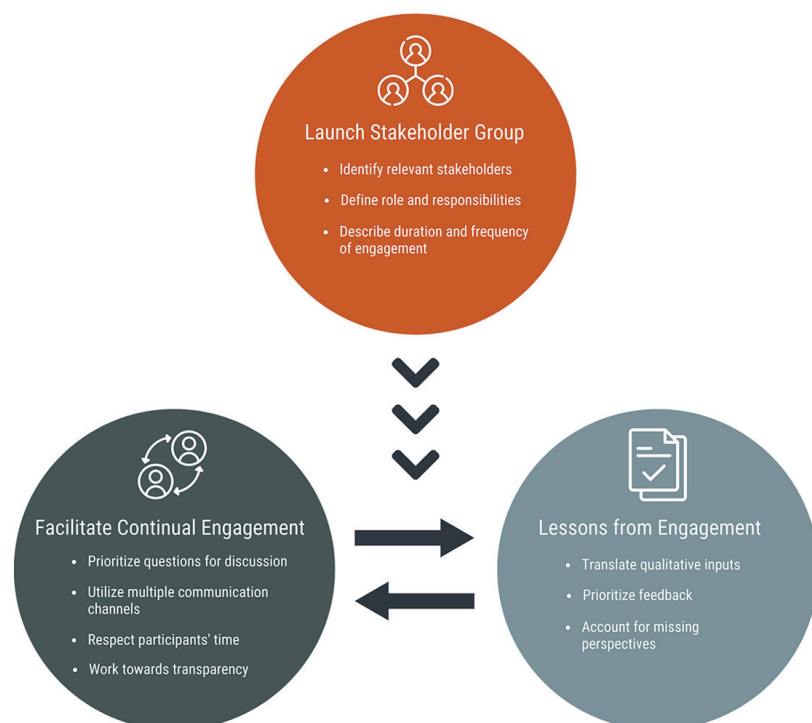
Another important aspect of "translation" lies in the use of appropriate explanatory methods and terminologies for different stakeholder groups. For example, the term "patient" may be commonly used by the HEOR community but may be rejected by people with the condition being considered. This requires researchers to be aware of such differences and actively solicit input on appropriate terminologies, types of information, and modes of communication to ensure full participation across stakeholder groups.

Prioritize Feedback

In aggregating feedback, we continue to explore how to prioritize suggestions from different stakeholders and, at times, reconcile conflicting perspectives. The specific criteria we have developed, based on the modeling objectives and the mission of the organization,⁶ include prioritizing: (1) recommendations with the broadest stakeholder buy-in, (2) recommendations from traditionally under-represented stakeholders (eg, patients and employers in our case), (3) recommendations that are most feasible to implement in the short-term, and (4) recommendations that are most likely to have policy- or decision-making impacts.

Since the development of OSVP models is an ongoing process, feedback that we cannot incorporate into the initial version of the model is identified for future model updates. We continue to work with the advisory group to ensure that the base model includes structural placeholders for such updates and design future studies that will generate key data to address those updates.

Figure 3. Key considerations for continual stakeholder engagement.



Accounting for Missing Stakeholder Perspectives

Research teams might not be able to recruit representatives from all desired stakeholder groups. In our case, despite best efforts, we do not have representatives from public payers or government agencies (eg, Centers for Medicare and Medicaid Services). Research teams can consider conducting individual outreach to these stakeholder representatives throughout the different phases. For example, we reached out to specific individuals who represent or have had extensive experience working with such stakeholders (eg, state Medicaid agencies) during the model scope public comment period to solicit specific feedback and will continue to do so in finalizing the model protocol and developing use cases.

Continuing Stakeholder Engagement

Applying a continual stakeholder engagement approach to economic model development has been an important learning opportunity for IVI and confirms our view that all value assessors should engage with diverse stakeholders early and often. Although certainly a complex and intensive

enterprise, the insights from the advisory group have already informed our model design, and have led to new partnerships and approaches to the model (**Figure 2**).⁵ Thus, we can affirm that stakeholder engagement has the potential to improve the value assessment methods and lead to economic models more useful and relevant to different stakeholders. Benefits accrue to the participants as well: through consistent engagement, the stakeholder participants also experienced direct exchange of experience and perspectives. While consensus for some key modeling considerations did not always result, such interaction increased learning about the viewpoints of each other and built trust in an open environment for closer collaboration in the future.

Closing Thoughts

Our next challenge is working with the advisory group to finalize the model protocol and validate the model prototype. Each interaction expands our thinking about the inputs, perspectives, and model functionality that are important to decision makers across the spectrum. And each is an opportunity to build our continuous learning, open-source model

development approach. In keeping with our principles, IVI will continue to share our experiences and real-time learning with the HEOR community to contribute to improved methods and practice in value assessment. Follow along at thevalueinitiative.org.

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Building Up What's Breaking Down: HTA in Latin America

A Conversation With Vania Canuto

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Photo courtesy of Vania Canuto

Q&A

I spoke with Vania Canuto, Director, Department of Management of Technology Incorporation and Innovation in Health, National Committee for Health Technology Incorporation (CONITEC), about some of the biggest obstacles to the implementation of health technology assessment in Latin America. Canuto has been working with the Brazilian Ministry of Health for more than 10 years.

“It is imperative to implement decision-making systems duly supported by scientific and economic evidence, whose results are investigated and analyzed using consistent methodologies.”

VOS: What do you believe are the most significant obstacles to health technology assessment (HTA) implementation in Latin America's low- and middle-income countries?

VC: The existence of health policies that encourage the decision-making process based on evidence is the first step towards the implementation of HTA in the country. In this sense, it is necessary to broaden the debate on the subject in Latin American countries. All actors involved need to be aware of the important role of HTA as a tool for the efficient use of health resources and to promote access to more effective technologies that are adequate to the real needs of patients.

In this sense, in 2008, the Brazilian Ministry of Health created the Brazilian Health Technology Assessment Network, which has made substantial efforts to contribute to the formation of Health Technology Assessment Centers. These centers seek to introduce the HTA culture in universities, hospitals, and other public health establishments. In this regard, we can highlight the work of the Red de Evaluación de Tecnologías Sanitarias de las Américas in order to bring together actors and stimulate the debate and implementation of HTA in Latin American countries.

But undoubtedly, in addition to the underfunding of health systems, one of the biggest obstacles to the implementation of HTA in Latin America is the shortage of trained professionals. Both the Brazilian Health Technology Assessment Network and the Red de Evaluación de Tecnologías Sanitarias de las Américas have promoted and fostered training in the area, but the need for qualified labor still persists.

In the United States, HTA has been used by some health insurance companies and large hospitals for a long time, despite not having a public health system. However, HTA has less space in a market-oriented health system where the consumer/patient pays directly for a given health technology.

VOS: Have health policies changed in the past 5 years?

VC: At the beginning of 2022, two changes in the regulatory framework for health in Brazil will contribute to the development of HTA in the country.

The first, Law no. 14,307, passed on March 3, 2022, introduced the use of HTA and the predictability of deadlines in the process of updating coverage in the field of private health, and instituted the Commission for Updating the List of Procedures and Events in Supplementary Health.

The second was the approval by the national Congress of a bill that determines that the methodologies, indicators, and cost-effectiveness parameters used in the economic evaluation of the process of analyzing the incorporation of technologies in the Sistema Único de Saúde by the National Committee for Health Technology Incorporation be set out in regulation and widely disseminated.

VOS: Is universal health coverage gaining or losing ground in the governments of the Americas?

VC: During the pandemic we observed the appreciation of the Sistema Único de Saúde, our public health system, by the Brazilian population and a significant expansion of the debate around public health and the guarantee of universal access to healthcare. Successful healthcare systems such as the United Kingdom and Canada show that the universal public system is more rational and efficient. In this sense, researchers and management bodies have been dedicated to improving decision-making processes and seeking to promote evidence-based health policies that actually meet the needs of users. In addition, we see the expansion of dialogue between countries in order to create strategies that address territorial needs and also the creation of manuals and guidelines for good practices in HTA, in addition to the exchange of experiences and knowledge between Latin American countries.

VOS: How can we create a sustainable health system with premium prices for rare diseases?

VC: This is undoubtedly an important challenge, especially in the context of health systems with limited funding, as is the case in most Latin American countries. We have observed a significant increase in the prices of new technologies for these diseases and the available studies do not allow us to be sure of the real benefit they will bring to the patient. It is increasingly essential to assess the opportunity cost and the impacts that high prices can produce in a health system with such limited resources.

Given this, 2 actions do not fully resolve the issue but can help to mitigate it. On the one hand it is important that the technologies incorporated for rare diseases have their effectiveness evaluated through information systems and real-world studies, given the disruptive nature of these technologies and the innovations that have been increasingly present. On the other hand, measures such as risk-sharing agreements can also prove to be a potent alternative. In any case, the central effort must be to offer the population the most effective therapeutic alternative, without the inappropriate use or investment of public resources in less efficient technologies than others.

In addition to the underfunding of health systems, one of the biggest obstacles to the implementation of HTA in Latin America is the shortage of trained professionals.

VOS: How do you view the Latin American countries' fragmented health systems?

VC: The issue of the fragmentation of health systems seems to permeate, to a greater or lesser degree, the reality of different Latin American countries. This fragmentation between subsystems and levels of care can lead to increased inequity and disparities in health, as well as losses in terms of the quality and effectiveness of health policies. Even in Brazil, where we have a decentralized, regionalized, and hierarchical health system, we observe difficulties in the interaction between the levels of care. An example of this is the process of incorporating technologies, which can involve several obstacles and depending on the region, the budget amount, the infrastructure already available, etc. In this sense, a robust situational analysis is necessary to detect by what means and in what way the fragmentation is established, and in turn establish priorities so that an integration strategy can then be adopted to optimize the use of health resources.

VOS: What can we do as HEOR researchers to make an impact on healthcare policy at a local, regional, or national level?

VC: It seems to me to be of fundamental importance that researchers dedicated to economics and health outcomes are in close contact with managers and public health policy bodies at the local, regional, and national levels. It is imperative to implement decision-making systems duly supported by scientific (quantitative and qualitative) and economic evidence, whose results are, in turn, investigated and analyzed using consistent methodologies. With this, it is possible to establish a virtuous cycle of creation, evaluation, and improvement of public health policies that accompany the technical-scientific development in the area.



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