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VALUE & OUTCOMES SPOTLIGHT

A magazine for the global HEOR community.

EXPANDING THE VALUE CONVERSATION

ISPOR
Improving healthcare decisions

VALUE & OUTCOMES
SPOTLIGHT

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The mission of *Value & Outcomes Spotlight* is to foster dialogue within the global health economics and outcomes research (HEOR) community by reviewing the impact of HEOR methodologies on health policy and healthcare delivery to ultimately improve decision making for health globally.

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FEATURE

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FROM THE EDITORS

Stakeholder identification is critical when embarking on a comprehensive health economic evaluation. However, that step itself is insufficient without fully engaging with these stakeholders and understanding both their overall perspectives and particular priorities within the healthcare system, including their specific interests related to treatments or programs under evaluation. What are their financial stakes and how are they held accountable for optimizing patient outcomes or, as is the case with patient stakeholders, how can they hold other organizations accountable? What is their role in shaping or influencing decisions regarding who should get the treatment and at what cost?

This issue focuses on stakeholders and begins with a primer titled, "Expanding the Value Conversation," which summarizes their role in value-based healthcare decision making. This article, authored by John Watkins, PharmD, MPH, BCPS, is the first in a series that focuses on stakeholders and their perspectives. As perspective is key to the success of our discipline, future articles published in *Value and Outcomes Spotlight* will feature articles on payer, patient, and provider stakeholders through commentary on contemporary topics or invited or ad hoc stakeholder-relevant submissions.

This issue also includes an article authored by colleagues from the National Health Council and focuses on tools for compensating patients for their engagement in health-related research. As arguably the most important healthcare stakeholder, patients need to be recognized and appropriately compensated for their integral role in and contributions to outcomes research, whether those contributions include providing relevant perspectives or data directly to our research rather than obtaining information through other proxy sources.

Finally, the issue contains an article by Desai and colleagues on the need for healthcare stakeholders to identify "fit for purpose" real-world data for HEOR evaluations. In a sea of data derived from electronic health records, administrative/billing records, disease registries, genetic profiles, digital apps, and other sources, can we identify a core set of measures and establish criteria for assessing data quality? The Use-Case specific Relevance and Quality Assessment (UReQA) framework introduced by the authors provides one model for making that assessment.

As always, we welcome the input of our readers, especially as it relates to stakeholder perspectives in value assessment. Please feel free to contact us by emailing zeba.m.khan@hotmail.com or laura.pizzi@rutgers.edu.

Zeba M. Khan, RPh, PhD and
Laura T. Pizzi, PharmD, MPH
Editors-in-Chief, *Value & Outcomes Spotlight*

ISPOR SPEAKS

There Is Light at the End of the Tunnel

Jens Grueger, PhD, ISPOR President 2020-2021, Director and Partner, Boston Consulting Group, Zurich, Switzerland

My presidency of ISPOR was very different from what I had expected. I think back to ISPOR Europe 2019 in Copenhagen, our last face-to-face meeting before the pandemic. As the President-Elect, I was shadowing then-President Nancy Devlin and learned what it meant to follow as her successor. Almost 6000 participants; full houses for our plenaries, issues panels, spotlight sessions, and oral sessions; busy exhibitor halls; and fantastic poster sessions. I met old and new friends and colleagues from all over the world, from a variety of backgrounds, all excited to connect, share their experiences, and learn from others.

> I started my presidency sitting in my office at home, glued to the Zoom/Teams/WebEx screen, making sure I was not on mute when I wanted to say something, struggling with frozen screens, and bad audio, and trying to figure out how to share my screen.

And then the first reports about COVID-19 emerged from Asia, cases were diagnosed in North America and Europe, and we closed down our office in Zurich in early March 2020 after 2 colleagues contracted the virus. ISPOR 2020, which was planned for Orlando, had to be transformed to a virtual meeting at the last minute without any prior experience with how to run such a meeting online. We learned, improvised, and while there were a few bumps along the way, it worked.

I started my presidency sitting in my office at home, glued to the Zoom/Teams/WebEx screen, making sure I was not on mute when I wanted to say something, struggling with frozen screens, and bad audio, and trying to figure out how to share my screen. I had to remind myself that while I was in sessions at odd hours of the day or night, it was still less stressful then traveling halfway around the world, dealing with jet lag and dry skin to attend a conference. And I did not have to run from one end of the conference hall to the next and then risk having to stand at the back of the room. Just a few clicks and I was in the next session. When I could not decide which of the parallel sessions to attend, I could replay them easily the day after. I did not meet people in the queue for coffee, but I could chat with them while my Nespresso machine was making me a fresh pot.

Don't get me wrong, I am very much looking forward to having face-to-face meetings again, but it was an interesting experience being your first virtual ISPOR President.

My focus as ISPOR President changed due to the pandemic. For ISPOR, it was all about acting fast, accelerating our digital transformation, and ensuring that we manage the unpredictable financial situation. I was lucky and privileged to be able to work with such an experienced CEO and Executive Director, Nancy Berg, and a very talented and diverse Board of Directors. The ISPOR staff all went the extra mile to support members, directors, chapters, work groups, and conferences, as well the ongoing operations, and I want to thank them all for this. Despite the significant financial loss on our operations, we ended 2020 in a better financial situation than we could have hoped for, thanks to insurance coverage, workforce protection programs, and of course, painful cost cutting.

My vision as ISPOR President included 3 priorities: (1) advancing the science of health economics and outcomes research (HEOR) to address innovative treatment options; (2) broadening the reach of ISPOR to expand capacity for health technology assessment (HTA) and HEOR in low- and middle-income countries (LMIC); and (3) building the leadership pipeline within ISPOR. We have made significant progress on all of these:

- **Innovation**: Digital technologies have changed the scope of healthcare and the scope of ISPOR. We have seen an increase in digital healthcare, both in the way care is delivered as well as the acceleration in digital technologies, including biomarkers and therapeutics that require new approaches to assessing and monitoring healthcare technologies.
- **Emerging markets**: In 2020, ISPOR programs were utilized by people from more than 120 countries. The Society has retained robust LMIC member engagement even in the face of the pandemic. We have formed a work group to further advance our strong LMIC engagement and future strategies, including a new LMIC HEOR Excellence Award.
- **Leadership development**: Focus on this priority has ensured a pipeline of future leaders and continuation of our diversity commitments that are vital to our ability to be our best and a respected society. New mid-career members have joined the Health Science Policy Council and other groups. Engagement of students, new professionals, and mid-career members remains a priority.

Looking back at my term as ISPOR President, a number of things stand out:

- We are a resilient Society that is able to adapt to changes rapidly, even when they are as extreme as what we have experienced with the COVID-19 pandemic.
- The mission of ISPOR around improving healthcare decision making is more relevant than ever, as we saw a few weeks ago during our Annual ISPOR 2021 meeting, where our plenaries and many other sessions highlighted the importance of resilient healthcare systems, being supported by data and models, taking a broad perspective on value to improve outcomes for patients.
- While I have not yet met anyone who says that virtual is better than in person, I believe that the push for digitalization in our private and work lives, as well as in our conferences, will stay with us and give us more efficiency and flexibility regarding how we participate and share in the dialogue at our conferences, in particular for those of us who cannot travel to ISPOR meetings.

I had my second vaccination in May. I know that this is a privilege and not all of you are already at that stage, in particular those of you outside of North America and Western Europe. But there

> We are a resilient Society that is able to adapt to changes rapidly, even when they are as extreme as what we have experienced with the COVID-19 pandemic.

is light at the end of the tunnel. More vaccines are available in ever-increasing quantities, we are opening up schools, restaurants, sports clubs, and businesses, and I look forward to seeing you all again in person soon at one of our conferences.

HEOR NEWS

1 AbbVie Exploits US Patents to Protect Profits: Congress Report

(PharmaLive)

According to a US House of Representatives Oversight Committee staff report, drug maker AbbVie exploited the US patent system to push up prices for its Humira® (adalimumab) rheumatoid arthritis drug and Imbruvica® (ibrutinib), a cancer drug. The committee called Humira "the highest grossing drug in the world."
Read more.

2 How One Startup Is Turning Unwieldy Health Records Into a Patient-Friendly Platform

(STAT News)

PicnicHealth says its mission is to make it possible for users to access all of their medical encounters, no matter how unwieldy the format. The company has built a system to let its users focus on self-care rather than data management.
Read more.

3 Cancer Outcomes Among Medicare Beneficiaries and Their Younger Uninsured Counterparts

(Health Affairs)

A study published in the May 2021 *Health Affairs* assesses cancer survival differences between uninsured patients younger than 65 and older Medicare beneficiaries by using data from the National Cancer Database from the period 2004–2016. The study found that compared with older Medicare patients, younger uninsured patients had strikingly lower 5-year survival across cancer types.
Read more.

4 Modernized Clinical Trials Include Diverse Representation, Decentralization, and Real-World Data in Post-COVID-19 Era

(OncLive)

The COVID-19 pandemic has opened the door for new opportunities for decentralized clinical trials and real-world data in a post-COVID-19 world, according to a panel discussion.
Read more.

5 A Clinical Trial Coordinator Is Indicted for Falsifying Data in a Glaxo Asthma Drug Study

(Pharmalot)

A former study coordinator at a company hired to run a clinical trial of a GlaxoSmithKline asthma medication has been indicted for falsifying data. Jessica Palacio, 34, worked at Unlimited Medical Research, which is based in Miami and was one of several companies tapped to help with a study designed to assess the safety and effectiveness of Advair Diskus® (fluticasone propionate) for children between 4 and 11 years old, according to court documents.
Read more.

6 Future Health Index 2021: Healthcare Leaders Look Beyond the Crisis

(Royal Philips)

Royal Philips has released its annual Future Health Index report, which this year explores how healthcare leaders are meeting the demands of today as they prepare for an uncertain future.
Read more.

7 Use of Real-World Evidence in Economic Assessments of Pharmaceuticals in the United States

(Journal of Managed Care and Specialty Pharmacy)

While real-world evidence (RWE) has been commonly used to inform pharmaceutical value assessments conducted by ICER, a study in the January 2021 *Journal of Managed Care and Specialty Pharmacy* found that there has been relatively limited use of RWE to inform drug-specific effectiveness, despite calls for greater inclusion of RWE in value assessments for real-world drug effectiveness.
Read more.

8 Report Provides Examples of RWE in Medical Device Regulatory Decisions

(Policy & Medicine)

The US Food and Drug Administration's Center for Devices and Radiological Health has issued a report that looks at how RWE sources can be used to support marketing applications for medical devices.
Read more.

9 RWE on Biosimilar Adherence and Adoption

(American Journal of Managed Care)

Posters from the Academy of Managed Care Pharmacy annual meeting evaluated RWE on adherence to biosimilars and barriers to biosimilar adoption. While patients on reference drugs had higher persistency, patients on biosimilars were more adherent to the medications, according to one of the posters presented.
Read more.

10 Senate Finance Panel's New Legislative Staffer Kaltenboeck Likes Quality-Adjusted Life Years For Valuing Drugs

(The Pink Sheet)

The Pink Sheet's Kathy Kelly looks at Anna Kaltenboeck, the new legislative staffer joining the committee from Memorial Sloan Kettering's health policy group.
Read more.

FROM THE JOURNALS

When Patient Health Interventions Affect Their Carers

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

Guest Contributor: **Marisa Santos, MD, PhD**, HTA Unit/Instituto Nacional de Cardiologia, Rio de Janeiro, Brazil

Inclusion of Carer Health-Related Quality of Life in National Institute for Health and Care Excellence Appraisals

Pennington BM

***Value Health.* 2020;23(10):1349–1357**

Some diseases that seriously affect children and the elderly cause significant limitations for family carers. These reduce the quality of life and create depression, anxiety, and other health consequences of bereavement. Dementia, mainly Alzheimer's disease, affects an estimated 10% of people over 65 in the United States. The familial caregivers are the ones mainly responsible for most patient care, suffering both psychological and physical burdens. Being a caregiver has even been identified as a risk factor for mortality. Besides anxiety and depression, caring for a relative with dementia reduces recreation time and increases work and family conflicts.

To measure the quality of life, many agencies preferred generic multiattribute utility instruments, such as the Health Utilities Index (HUI), the 36-item short-form survey, or the Assessment of Quality of Life. The National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium prefer EQ-5D for adults, with few exceptions. Usually, the appraisals measure only the patient's quality of life, but the documented spillover burden on carers can be included in the cost-utility analysis, theoretically creating a fair model. If spillover effects are not measured, the real technology benefit can be underestimated. The literature and some agencies like NICE accept the inclusion of health-related quality of life (utility values) for situations where the carer impact is evident.

Utility measures of health-related quality of life are preference values that patients attach to their overall health status. In clinical trials, utility measures summarize both positive and negative effects of intervention into one value between 0 (death) and 1 (full health). These measures allow for comparison of patient outcomes of different diseases and between various healthcare interventions. This article reviewed NICE technology appraisals and highly specialized technologies reports looking for the search terms "carer" or "caregiver." The objective of the study was to describe and discuss: (a) sources of evidence of carers' health-related quality of life; (b) how the carers' data have been included in the analysis and how they affected the results and; (c) if the decision makers considered carers' data relevant for the final decision.

From a total of 422 reports, 16 included carer quality-of-life data. In another 11 reports, the committee discussed the topic, but the data were not included in the economic analysis. In many appraisals (46 of 422), the committee discussed impact on carers, but not in the context of health-related quality of life. The diseases where carers' data were part of cost-utility models were: multiple sclerosis, Alzheimer's disease, juvenile idiopathic arthritis, atopic dermatitis, myelofibrosis, mucopolysaccharidosis type IVa, Duchenne muscular dystrophy, adenosine deaminase deficiency-severe combined immunodeficiency, and X-linked hypophosphatemia.

One source was utilized for more than 1 appraisal; 16 appraisals adopted 5 sources. The sources used had been produced in different countries, and 3 of 4 sources used the EQ-5D questionnaire. The values for EQ-5D for carers varied from an increase of 1% to a decrease of 17.3%.

One of the studies included in the review was by Neumann et al[1] for Alzheimer's disease. There was the supporting evidence for one Alzheimer's disease appraisal, 7 multiple sclerosis appraisals, 1 mucopolysaccharidosis type IVa, and juvenile idiopathic arthritis, and was based on the HUI classification system. Neumann estimates the difference between full health and the worse state resulted in 14% loss of quality of life for carers (0.14 disutility).

Regarding methods for including carer quality of life into cost-utility data, all the appraisals used secondary data from literature and modeling the impact of the intervention on patients' health and the estimated effect on carers' quality of life. The cost-utility models included the carers' quality of life losses (disutilities) related to the patient disease severity or death. The number of appraisals, including carer quality of life, increased over time.

Unfortunately, only 10 quality-adjusted life years (QALY)/Institute for Clinical and Economic Review (ICER) results are open access; the others were confidential or not presented in the final report. As expected, the inclusion of the carers' quality of life reduced the ICER and increased QALY results. The impact on QALY, in general, was considered low (less than 0.03 QALYs). The more significant effect was achieved in the moderate/severe atopic dermatitis, decreasing ICER by £9498. The percentage change in QALY was from 0 (mucopolysaccharidosis type IVa) to 22% (multiple sclerosis). The reduction in the ICER values was from 4% (juvenile idiopathic arthritis) to 33% (moderate to severe atopic dermatitis).

In most decisions (11 of 16), the committee agreed to include the carer quality-of-life data in the base case. The reasons for

excluding the carer data were the absence of robust data and a preference to judge using only qualitative information about the carer impact. The authors concluded the need for more evidence with better quality.

The paper showed that, although foreseen in several technical manuals and the British Agency documents, the inclusion of carers' utility values in economic models is still not a routine. Most models do not numerically count these effects, even for diseases with recognized impact, especially on carers' mental health. Knowing that this information represents a gap in the current reports may indicate a space for improvement. Health technologies assessment (HTA) agencies and governments should discuss routine inclusion of carers' health state utility values, adopting strict criteria for disease selection.

The paper is relevant for commitee members and health economists, revealing an opportunity to create better models, including the impact of severe diseases on carers' quality of life. For other points of view, the collected information showed that this approach's primary limitation is data availability, an opportunity for HTA researchers. For conditions with a high degree of carer burden, interventions that improve patient quality of life reduce the need for carer time and improve carer quality of life. Models with this information usually have lower ICERs, favoring the incorporation of essential technologies. Carers' quality of life brings a small part of societal economic impact, most of the time forgotten by decision makers.

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FROM THE REGIONS

A Review of 2021's Top Global HEOR Trends: Perspectives From the ISPOR Global Groups

Robert Selby, MBA, Director, Global Networks, ISPOR, Lawrenceville, NJ, USA

To better understand how global health economics and outcomes research (HEOR) priorities are shifting through the COVID-19 pandemic, ISPOR conducted a survey among leaders within some of the ISPOR global groups to assess their perspectives on what the top HEOR trends are for the regions in 2021. As part of their annual meeting agendas, executive committee members of the ISPOR Asia Consortium, Latin America Consortium, Central and Eastern Consortium, Arabic Networks, and Africa Networks were asked to share the top 3 HEOR topics for their respective regions or work areas. The survey was not intended to be an exhaustive investigation but rather an interesting exercise to shed more light on global perspectives from ISPOR global leaders.

The **Figure** below shows the distribution of top trending topics by region as reported by the leaders.

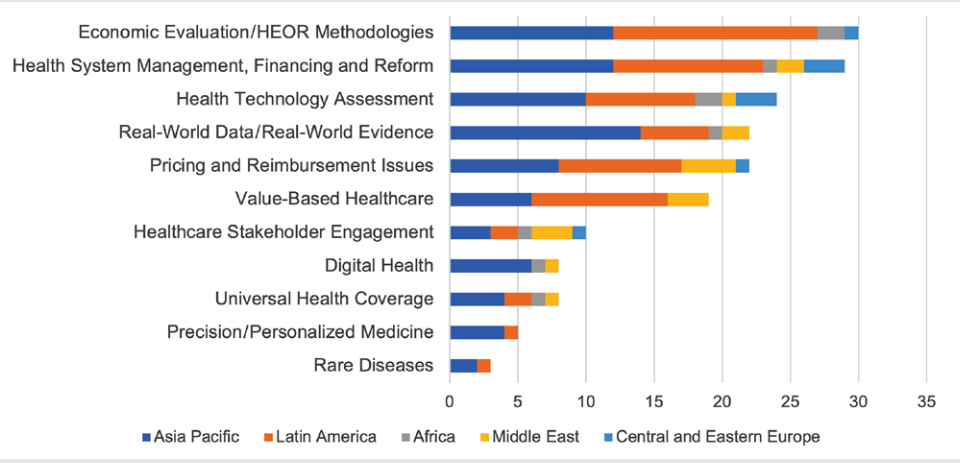
Methodology

A total of 101 people were surveyed with 67 responding. The Asia Pacific region accounted for nearly 45% of the total responses, with 34% from Latin America, 9% from Africa, 9% from the Central and Eastern Europe region, and 10% from the Middle East. The survey yielded 160 individual topic suggestions, with 50% of the suggestions from the Asia Pacific region, 35% from Latin America, 9% from the Middle East, 6% from the Central and Eastern Europe region, and 6% from Africa. (Note: It is acknowledged that this exercise is limited by the uneven distribution of responses from the regions, which presents bias in the results toward the response-heavy regions, namely Asia Pacific and Latin America.)

The individual topic responses were grouped into 11 categories. Recommendations relating to general HEOR methodologies and particularly, economic evaluation practices were grouped into the category "Economic Evaluation/HEOR Methodologies." There were also broader categories encompassing health system management, financing and reform, and pricing and reimbursement issues. "Value-Based Healthcare" was listed as a separate topic from "Pricing and Reimbursement Issues," due to its emergence as a widely acknowledged novel concept that also covers healthcare delivery.

The **Table** shows examples of specific topic suggestions within the broader categories.

Figure. Top 2021 global HEOR trends as reported by ISPOR regional consortia and network leaders.



HEOR indicates health economics and outcomes research.

Adapting HEOR Core Methodologies to New Paradigm

As healthcare and health systems undergo radical transformation through the effects of the COVID-19 pandemic and disruptive technological innovation, ISPOR regional leaders have prioritized the adaptation of economic evaluation and other core HEOR methodologies to be more fit-for-purpose for the real world. Crucially, this topic has also been identified as a strategic priority for the recently published ISPOR Science Strategy. Specific issues raised include revisiting traditional measures that estimate quality of life and health state utility, specifically for children and other special populations, and ICER thresholds and assumptions surrounding opportunity cost versus willingness to pay (societal vs individual). More generally, countries in need of foundational HEOR capacity require the development of national pharmacoeconomic guidelines, and countries with existing guidelines should update them regularly. Recently, Hungary's National Department of Health established a Guideline Revision Committee to update the "Guideline for Economic Evaluations in Healthcare in Hungary," and to lay out new recommendations for a revised cost-effectiveness threshold in the country.[1] In China, the most recent iteration of pharmacoeconomic guidelines was published in 2020, which updated and added to foundational frameworks in place from the previous version, drawing on the latest research in pharmacoeconomic evaluation, adapting practices to a societal view, and incorporating a broader range of therapies including traditional Chinese medicines. However, developing accurate health utility measures for Chinese subpopulations has remained a challenge for research going beyond traditional cost-effectiveness analysis.[2]

Strengthening Regional Health Systems

Even prior to the pandemic, many countries' health systems were struggling to deliver optimal health outcomes for patients in the face of severe budget constraints, given the

Table. Top 2021 HEOR global trends and subtopics as reported by ISPOR regional consortia and network leaders.

Economic Evaluation/HEOR Methodologies
- Role of HEOR in the COVID-19 pandemic
- Cost-effectiveness of COVID-19 treatments
- Opportunity cost vs willingness to pay (societal vs individual)
- Estimating QoL and utility weights for children
- ICER threshold utilization
- Complementary and alternative medicine evaluation
- Pharmacoeconomics guideline development
- Local multiattribute utility instruments development

Health Systems Management, Financing, and Reform
- Novel financing mechanisms for healthcare
- Formal and informal healthcare spend considering resource constraints
- Methods for priority setting in healthcare delivery
- Health system sustainability
- Rebuilding health systems for crisis response
- Health policy and budgeting for noncommunicable diseases
- Vaccination programs
- Deferred care in the pandemic era

Health Technology Assessment
- HTA of COVID-19 therapies
- Hospital-based HTA
- Influence of human rights regulations on HTA outcomes
- Transparency of HTA processes
- HTA in value-based healthcare environments
- HTA's role in reducing health expenditure
- Transferability of HTA across jurisdictions
- HTA of medical devices
- Implementing HTA in emerging countries
- Multicriteria decision analysis

Real-World Data/Real-World Evidence
- Patient-generated data utilization
- Access to data
- Big data/machine learning methods for HTA and economic evaluation
- National RWE guidelines
- RWE for regulatory and reimbursement decision making

Pricing and Reimbursement Issues
- Pricing of essential generic medicines
- Drug pricing transparency
- Pricing policies in the pandemic era
- Vaccine pricing
- Novel approaches for patient access to innovative/high-cost technologies

Value-Based Healthcare
- Value frameworks
- Managed-entry/risk-sharing agreements
- Value-based healthcare in the pandemic era
- Value-based contracting

Healthcare Stakeholder Engagement
- Patient advocacy groups, engagement
- Multistakeholder involvement in healthcare decision making

Digital Health
- Digitalization of health for cost-effective delivery of health services in developing countries

Universal Health Coverage
- Access and equity

Precision/Personalized Medicine
- Rapid development and introduction of genomics and personalized medicine into health systems

Rare Diseases
- Policies for access to therapies

HEOR indicates health economics and outcomes research; ICER, Institute for Clinical and Economic Review; HTA, health technology assessment; RWE, real-world evidence.

growing burden of chronic disease and the proliferation of expensive innovative therapies. The pandemic has exacerbated these challenges, simultaneously derailing economic growth and putting tremendous financial pressure on public health entities to finance crisis response and vaccination programs. Many countries have had to rebuild their health systems, make them more efficient, and find new ways to prioritize spending. In Latin America, a need for novel financing mechanisms for health systems is leading to innovative approaches, including results-based financing initiatives such as Argentina's Plan Nacer/Programa Sumar, and impact funds supported by nonprofit entities, corporations, and investment banks such as the UNICEF Bridge Loan Fund.[3] Centralized procurement has emerged as a key tool for cost savings, with China implementing their "4+7 Plan" for generics and Mexico developing a national compendium that established standard formulary bidding, procurement and health technology assessment (HTA) processes across the country's health institutions.[4,5] In the Middle East, public-private partnerships are increasingly seen as a viable strategy to improve the performance of health systems by bringing together the best characteristics of the public and private sectors to improve efficiency, quality, and innovation.[6]

Pricing and Reimbursement Issues

Pricing and reimbursement remain a highly important topic for global leaders, particularly around the aspects of transparency and access to therapies. In particular, how governments are enabling broader access to COVID-19 therapies and how the pricing is determined are of great interest. In a bid to support broader access to COVID-19 vaccines in lower- and middle-income countries, governments in India and South Africa raised a proposal last year for consideration by the World Trade Organization to waive intellectual property protections on COVID-19 vaccines and treatments. No formal decision has been made yet on this by the council, with further discussion expected at their meeting in June. As more countries reassess their positions on this issue, the ongoing discussions could provide impetus for reorientation toward greater global collaboration on equitable access to therapies.[7]

Other countries are taking proactive steps to update their own national reimbursement drug lists. In China, the National Healthcare Security Administration in 2020 established a dynamic update mechanism of the National Reimbursement Drug List, which provides for annual reviews and updates. A national drug price negotiation mechanism between the government and the pharmaceutical companies was also formally introduced in China in 2017, which has centralized negotiations around pricing and reimbursement.[8] The introduction of high-cost innovative therapies, including curative and gene therapies, is also necessitating novel approaches to reimbursement and access, including managed-entry/risk-sharing schemes, mortgage or subscription payment models, indication-specific or value-based pricing, and other value-based contracting approaches.[9] In South Korea, financial-based risk-sharing agreements have increased markedly in prevalence (there were 11 risk-sharing agreements in 2016 compared to 35 risk-sharing agreements in 2020), and a coverage expansion policy by the National Health Insurance program has led to an increase in the overall coverage rates for interventions, where

provisions are made for selective or preliminary coverage of novel therapies with subsequent evidentiary development over a 3- to 5-year timeline.[10]

HTA's New Challenges

HTA has faced new challenges in the wake of the pandemic, forcing traditional processes and roles to adapt to new settings and requirements. HTA bodies have had to rapidly evaluate and approve interventions that may not have sufficient clinical or cost-effectiveness data available. In Latin America, a lack of readily available local evidence has led to changes in evidence sourcing, with the recently established Regional Database of Health Technology Assessment Reports of the Americas (developed jointly between Health Technology Assessment Network of the Americas and the Pan American Health Organization) serving as an important resource for the region. In Mexico, HTA is being used as a tool to support prioritization and rational use of health resources and to maintain sustainable healthcare budgets.

Specific emphasis is being placed on expanding hospital-based HTA to cover all medical technologies and treatment pathways in the hospital setting.[5] Many countries are in the process of establishing new HTA units or agencies or strengthening existing HTA bodies. Japan's new HTA unit, the Center for Outcomes Research and Economic Evaluation for Health, which was established in April 2019, has begun releasing their first public economic evaluation reports after an extensive pilot program.[11] In the Ukraine, efforts are ongoing to strengthen processes and legal frameworks to make HTA more sustainable, reliable, and independent, and clarify the role of HTA in the transition towards a national positive list for reimbursement.[12] Other issues, such as the transferability of HTA across jurisdictions and HTA of medical devices, remain important priorities for global HEOR.

Additional Topic Considerations

Subsequent topics seemed to vary in importance across the different regions. In the Asia Pacific, real-world data, digital health, and precision medicine were ranked higher in priority, while in Latin America, value-based healthcare and universal health coverage ranked higher. In Europe, the Middle East, and Africa, healthcare stakeholder engagement was ranked higher, specifically referring to patient advocacy groups, engagement, and multistakeholder involvement in healthcare decision making. These variances could reflect the level of capacity or development in the regional systems or could just be a product of the survey population's skew. Further investigation along these lines could yield interesting results.

We welcome your further thoughts and input! To send your comments about this article or for more information and to join ISPOR global groups, please contact globalgroups@ispor.org.

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ISPOR NEWS

COVID-19: Challenges and Opportunities for the Global Health Technology Assessment Community

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The COVID-19 pandemic has disrupted global healthcare systems and created significant challenges for the health technology assessment (HTA) and payer communities.[1] To better understand these challenges, ISPOR conducted a qualitative survey involving all participants of the ISPOR Regional HTA Roundtables. In this article, we present the results of these surveys and discuss the implications of the identified challenges and opportunities.

As described on the ISPOR website[2], the ISPOR Health Technology Assessment (HTA) Council is a global body of healthcare decision makers who advise the Society on ways to bridge the gap between outcomes research and healthcare decision making. One of the primary activities of the Council is the convening of HTA Roundtables. These roundtables provide a platform for technology assessors and payers to discuss issues related to the reimbursement of health technologies. Attendees include representatives from public and not-for-profit HTA agencies, public and private payer organizations, patient group representatives, and government-contracted academic centers (if no HTA body exists in the country). ISPOR convenes annual HTA Roundtables in the Asia Pacific region, Europe, Latin America, the Middle East and Africa, and North America.

The survey consisted of one open-ended question: "*What are the top three HTA/Payer challenges or opportunities that have surfaced during the COVID-19 pandemic?*" Respondents were asked to identify challenges and opportunities related to the diagnosis and treatment of COVID-19 and also to discuss how the pandemic has impacted HTA unrelated to COVID-19.

Main Challenges Identified

Results from the regional surveys were compiled in a rolling fashion and presented during each of the HTA Roundtables held in 2020. Global results and uniquely regional results were presented and discussed. Later roundtables received the benefit of being presented with a cascading summary of key challenges and opportunities identified in other regions. Following the final roundtable held on November 10, 2020, the results from all surveys were analyzed by the authors in consultation with other members of the HTA Council during a meeting held on December 9, 2020. The points presented below reflect the most pressing challenges common to all regions.

• *Speed Versus Quality:* During the pandemic—especially during the early months of the crisis—politicians, officials, healthcare providers, the media, and citizens had an insatiable appetite for answers. How does the disease spread? What protective equipment and public health measures should we employ? What diagnostic tests are available, and how accurate are they? What treatments are effective? Too many people were dying, hospitals were overflowing, and economies were crashing—governments and public health officials were under extreme pressure to remedy the situation with a prevailing attitude for them to "just do something." As a result, there seemed to be a never-ending requirement to provide evidence-based advice as rapidly as possible. HTA agencies responded by producing ultra-rapid reviews, conducting rolling reviews and updating reports as new evidence emerged, and increasingly used evidence-grading methodologies and processes for expert elicitation. Although there was concern from agency personnel regarding the quality and other risks associated with expedited reviews, the concept of ultra-rapid reviews has been well-received by policy makers and healthcare providers, and it is likely that there will be pressure to incorporate this type of review in the postpandemic environment.

> Too many people were dying, hospitals were overflowing, and economies were crashing—governments and public health officials were under extreme pressure to remedy the situation with a prevailing attitude for them to "just do something."

• *Economies in Distress:* Many survey respondents identified financial challenges as the most significant issue impacting their countries' ability to respond to the pandemic and to recharge their economies following the pandemic. Several mentioned that their country was already facing major economic burdens prior to the pandemic. To minimize the impact of lockdowns and business closures, governments offered substantial stimulus packages to individuals and businesses, adding further strain to their financial sustainability. This was further compounded with the need to procure protective equipment, diagnostic tests, treatments, and ultimately, vaccines. These fiscal challenges will extend well past the end of the pandemic, which should heighten the need for HTA as governments are faced with making tough choices on where best to allocate their scarce resources. The economic challenges could provide additional incentive to establish or augment HTA capacity in countries with limited formal HTA resources.

• *Accelerated Approval of Health Technologies:* During the pandemic, global regulators were under considerable pressure to expedite their approval of diagnostic tests, treatments, and vaccines designed to combat the virus. Most regulators have accelerated pathways to review breakthrough technologies, and they can provide special authorization or conditional approval. HTA practitioners, payers, and clinicians believe that accelerated approvals create significant uncertainty at market launch—uncertainty related to the comparative clinical benefit, harm, and value of the technology. Respondents to the survey indicated that during the pandemic, the reduced level of evidence for providing regulatory approval was creating even higher levels of uncertainty. There was also concern that some payers were bypassing HTA and going from regulatory approval directly to price negotiation (with some agreements being negotiated prior to regulatory approval). Rather than focusing on this as a growing risk, the HTA and payer communities should embrace concepts that promote early access to promising medicines and technologies by implementing a life-cycle approach to technology reviews. Key elements of life-cycle HTA include enhancing horizon scanning and early scientific advice; providing conditional reimbursement based on rolling reviews; implementing structured processes to collect and analyze real-world data[3]; reassessing technologies based on new evidence; employing risk-sharing initiatives via managed entry agreements; and developing innovative payment strategies.

> The totality of the public health burden of these diagnostic and treatment delays is uncertain; however, providers are concerned that there will be a major increase in morbidity and mortality.

• *Heightened Need for Harmonization and Collaboration:* During the pandemic, HTA agencies were inundated with requests to conduct reviews on a multitude of technologies, many of which went well beyond the scope of their prepandemic mandate. This included masks and other protective equipment, public health measures, ventilation systems, repurposing of drugs, vaccines and treatments for COVID-19, and a seemingly unending basket of diagnostic tests. Many respondents indicated that they struggled to stay ahead of the demand, while regulators, despite their own COVID-19 workload, were able to adhere to timelines by issuing market authorizations for a growing pipeline of novel non–COVID-19 drugs and technologies.

As reported in the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research annual report for 2020, there were 53 novel drugs approved, compared to 48 approved in 2019, and 68% of the novel drugs were approved under one or more of the FDA expedited pathways.[4] In Europe, the Human Medicines Highlights for 2020 summary from the European Medicines Agency (EMA) reported that the EMA issued 97 positive opinions, which included marketing authorization for 39 new active substances,[5] and a similar pattern emerged for regulators in other countries. Compounding the issue, many HTA agency staff were reassigned to clinical roles in hospitals or policy roles in government to aid in the management of the pandemic.

Even prior to the pandemic, a shortage of trained and experienced HTA practitioners was the number one challenge identified in a survey conducted by the International Network of Agencies for Health Technology Assessment in 2018.[6] HTA roundtable survey respondents stressed that they were forced to prioritize their workloads and, in some cases, had to suspend or delay non–COVID-19 work. This fostered a distinct shift to increased regional, national, and cross-border collaborations. As one respondent reported, "We were collaborating in areas where it felt forced prior to the pandemic." Respondents also signaled that there is a strong desire to continue to forge partnerships and promote harmonized approaches to market access once we move past the pandemic. However, to fully embrace collaboration, there will need to be a concerted effort by the HTA and payer communities to go beyond information sharing to encourage harmonization and build meaningful partnerships, perhaps building on a published summary of good practices in HTA.[7]

Could the World Health Organization (WHO) be engaged to develop HTA standards and practices, particularly for low- and middle-income countries? What lessons can be learned from collaborative initiatives established by the regulatory community? Regulators harmonize their processes and methods via the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, the International Coalition of Medicines Regulatory Authorities, and benchmarking by the Center for Innovation in Regulatory Science. Via these partnerships, regulators have developed structured approaches for "*Reliance*" (whereby a regulatory authority in one jurisdiction gives significant weight to work performed by another regulator) and "*Recognition*" (the routine acceptance of the regulatory decision of another regulator).[8] Should these models be replicated for HTA agencies and payers?

• *Assessing the Impact of Delayed Diagnosis and Treatment of Non–COVID-19 Diseases:* During the early stages of the pandemic, non–COVID-19 patient care was severely disrupted, and there was a significant shift to the provision of virtual care. The totality of the public health burden of these diagnostic and treatment delays is uncertain; however, providers are concerned that there will be a major increase in morbidity and mortality. What this means for the HTA and payer communities is unclear; however, it is expected that there will be requirements to reassess the effectiveness of treatments that were approved for use during earlier stages of a disease, to advise clinicians on new combinations and treatment regimens, and to review the impact of treatment delays on downstream healthcare costs. In addition, as patients have begun to appreciate the benefits of virtual care, there will be a need to assess the clinical effectiveness and value of these virtual approaches to healthcare.

Still More Challenges to Face

In addition to the issues mentioned above, there were a number of other challenges identified by survey respondents, including a confusing and competitive evidence ecosystem, especially in the early stages of the pandemic, as numerous organizations attempted to position themselves as the trusted source for evidence; supply chain challenges and drug shortages; an increase in the spread of misinformation (myths, rumors,

conspiracy theories), with many agencies using this as an opportunity to enhance their knowledge-sharing with members of the media and the general public; and there were equity issues associated with the hoarding of drugs and supplies and vaccine nationalism with wealthy countries purchasing the bulk of available supplies.

There were also challenges identified that were unique to a particular region. For example, respondents from the Asia Pacific HTA Roundtable expressed concern with their ability to meet the WHO targets for Universal Health Coverage during the pandemic, while participants from the Middle East and Africa worried that the pandemic would inhibit the growth of HTA in their region. Respondents to the North American roundtable included several comments related to inconsistent application of government regulations, removing preauthorization criteria, and providing a 60- to 90-day supply of medications to minimize patient travel to pharmacies.

Where Do We Go From Here?

This survey has identified some of the major challenges for HTA agencies and payers arising during the COVID-19 pandemic. Many of these challenges had their genesis prior to the outbreak, but they gained prominence during the pandemic. It also became clear that the pandemic may serve as a stimulus for change. Of note, the ongoing debate between speed and rigor will continue to flourish in the postpandemic environment. Regulators will continue to approve new drugs and devices using accelerated pathways with increasing levels of uncertainty; clinicians and patients will continue to demand early access to promising technologies; and policy makers will continue to push for timely HTA advice. To meet these challenges, life-cycle HTA, harmonization, and collaboration will need to be exploited. The ISPOR HTA Council will engage with stakeholders to further analyze challenges and advance opportunities arising from this survey.

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ISPOR GENERATES A *SIGNAL* FOR TRANSMITTING INNOVATION

Signal IN BRIEF

- The US Veterans Affairs Administration (VHA)—the largest integrated health system in the United States—has become an unexpected source of healthcare innovation.
- The VHA's ecosystem model approach to innovation empowers the workforce to be innovation agents.
- In just a couple of years, VHA Innovation Ecosystem programs saved $40 million through cost avoidance and directly impacted more than 1 million veterans.
- While governments are generally risk-averse to failure, failure is part of innovation. Allowing and learning from failure often leads to future success.
- The VHA has identified 4 critical elements needed to create a foundation for operationalizing innovation in a healthcare setting: (1) workforce capacity to actualize innovation, (2) resilient organizational infrastructure, (3) innovation-nurturing culture, and (4) strategic external partnerships and collaborations.

*The inaugural episode of ISPOR's new signature series, **Signal**, launched in April. The program is designed to look beyond today's linear thinking to explore topics that will shape healthcare decision making over the next decade. When speaking with ISPOR CEO Nancy S. Berg about the genesis of the **Signal** series, she acknowledged that the pandemic has been a main driver in forcing businesses to look for new opportunities for collaboration and innovation...and ISPOR was no exception. "The COVID-19 pandemic has driven all healthcare organizations to the realization that innovation is not optional—it's not a 'good to have,' it's a 'must do,'" Berg said. "We thought about what ISPOR and its members can do to improve the wider healthcare ecosystem and believe that the **Signal** series is a step in the direction of broadening our thinking, looking outward for ideas, and making HEOR part of fresh new approaches to innovation."*

Next Gen Innovation: A "How To" From the US Department of Veterans Affairs

The first ***Signal*** event highlighted a source of innovation from a place some might find surprising: the US Department of Veterans Affairs (VHA). While a target of criticism in past years, the VHA organization has proven itself as a true innovator. As explained by this ***Signal*** episode's speakers, Ryan J. Vega, MD, MSHA, Chief Officer, Healthcare Innovation and Learning, Veterans Health Administration and Kenneth W. Kizer, MD, MPH, Chief Healthcare Transformation Officer and Senior Executive Vice President, Atlas Research, the VHA's ecosystem has emerged as a model for supporting the entire life cycle of innovation in a large and highly complex integrated health system.

The VHA is the largest integrated healthcare system in the United States. There are 9 million enrolled veterans, with more than 1700 facilities across the country and in outlying territories, including 170 VA medical centers, 1074 outpatient facilities, and more than 500 community living, long-term care, and mental health counseling facilities. The large scale, closed system, and life-long care of its patients makes the VHA's experience and insights about innovation relevant and transferrable to other healthcare systems beyond the United States.

The Keys to Innovation

The VHA's ecosystem model approach to innovation combines product, process, and organizational structure together with continuous training and support, which empowers the workforce to be innovation agents. The model has produced programs aimed at the needs of veterans that both improve clinical outcomes and lower costs. Recognizing that challenges exist in how to estimate value when that value is often generated separately

from costs, the VHA used different cost-sharing mechanisms and bundling services to apply a total cost of care approach. The results? In just a couple of years, the VHA Innovation Ecosystem has engaged 25,000 employees and more than 150 facilities in innovation projects and activities. These programs saved $40 million through cost avoidance and directly impacted more than 1 million veterans.

Solutions That Make a Difference

In thinking about value, the VHA starts with purposeful innovation to create the solutions that deliver the most impact to veterans; then moves on to implementing those solutions through partnerships, investing in people, or scaling; and then measuring those. "Measurement gets a little bit tricky," Vega said, "because sometimes it's not just about the qualitative data that you get. It's also about the qualitative data—the voice of the veteran—telling us how valuable some solution is and that helps us get to the point that we are realizing value from these investments."

Because each project is unique, it has its own set of metrics and outcomes that are being targeted. "The ideation around the problem has to drive the solutions. Ultimately, the success of a solution is measured by its real-world impact," said Vega. The VHA has to take a very long view of veterans. "These are our patients, from the time that they transition and choose to come to the VHA and its care, to the time that they pass away. They're ours for those years and decades of their life." That means improvements can't be episodic—the VHA has to look at a veteran's life 5, 10, or 15 years after a change was made in the care delivery apparatus.

Looking to Front-Line Workers to Innovate

Due to the geographical spread of the VHA, it is reliant on the front lines to innovate. "While the system is administered in Washington, DC, how those policies get operationalized in Alaska isn't necessarily the same way as Florida or California, there's a lot of variability," Kizer explained. An integral part of the VHA is its teaching programs and research programs, making it a $2 billion a year research organization as well as the largest provider of training for other healthcare professionals including pharmacists, nurses, optometrists, and clinical psychologists.

One of the programs coming out of the VHA Innovation Ecosystem is a 10-week health education program developed for LGBTQ Veterans, called "PRIDE in All Who Served," that focuses on reducing healthcare disparities. Group facilitators follow a session-by-session manual with corresponding handouts on each topic. The manual includes information about how to access relevant services within the VHA system. Veterans who have attended the program have reported reduced likelihood of attempting suicide and reduced anxiety and concern about not being accepted. They also noted having an increased feeling of safety and protection through engagement in the community and certainty in their own identity.

While governments are generally risk-averse to failure, failure is part of innovation. Allowing and learning from failure often leads to future success. For example, a key component of the VHA's success is creating institutional memory around what worked, what didn't and why, and how this can be generalized through the system as a whole. While the future of healthcare innovation at the VHA may be bright, Vega cautioned there is also a lot of vulnerability. "When we look at things like remote patient monitoring, the idea that we can deliver more care in the home is incredibly exciting. But it also means an unbelievable amount of new data, which we don't know how to make much sense of today. Is it valuable to be continuously monitoring the heart rate of a veteran in their home? And once we say it is valuable, how do we make that information actionable intelligence for both the clinician and the patient?"

KEY TAKE-AWAYS

FOR HEALTHCARE INNOVATORS AND VALUE CREATORS:

- A whole health system approach—or ecosystem model—to innovation leads to transformative change at system level. This is the present-day requirement to innovative solutions, as it leads to improved clinical outcomes and lower costs.
- Next gen innovation = product innovation + process innovation + organizational structure innovation + workforce as innovation agents
- Real-world value (through clinical practice and patient experience) and replicability matters—it defines where and how innovation is supported
- Drivers of digital innovation in healthcare as seen by the largest integrated healthcare system in the United States:
  - "democratization" of healthcare space allows for the entrance of non-traditional players (eg, Facebook, Apple, Microsoft, Google, Amazon [FAMGA])
  - more healthcare services being provided in patients' home creates "increased convenience" as new quality/value parameter
  - new technologies create efficiencies in optimizing workflows, automating routines, and enabling remote monitoring outside of the healthcare setting

Digital technologies, enabled by 5G will bring a host of new opportunities, whether it's 3D holographic patient imaging in the operating room or simply improving navigating through a large healthcare system. "These technologies hold enormous promise, but to realize the value from them will take large collaborations, will take time, and will take meaningful, purposeful action to ensure that we are getting the value out of the technology and that the technology is not driving the workflow, the patients and the clinicians are," Vega said.

> "We talk about the VHA Innovation Ecosystem purposefully because we intend for it to operate as an ecosystem. It is composed of several portfolios, each unique and focused on various aspects of the innovation life cycle, but that come together to make this collective ecosystem thrive."
>
> — Ryan J. Vega, MD, MSHA

In summary, the VHA has identified 4 critical elements needed to create a foundation for operationalizing innovation in a healthcare setting:

Workforce Capacity to Actualize Innovation: Investing in VHA employees to give them the tools and skillsets needed to bring innovative ideas to fruition

Resilient Organizational Infrastructure: Institutionalizing innovation through integrated, systematic, repeatable pathways for change

Innovation-Nurturing Culture: Shifting the mindset to envision innovation as everyone's responsibility to improve service delivery and create a better new normal

Strategic External Partnerships and Collaborations: Innovation cannot be realized in isolation and requires novel, cross-industry partnerships that surface novel ideas and help catalyze a shift in the status-quo

The Next *Signal* Program

Signal episodes are scheduled throughout the year and will feature conversations with speakers who are innovative thought leaders and change makers in both healthcare and other sectors of economy, science disciplines, and areas of human inquiry that can impact healthcare.

The next ***Signal*** event, "From Price Determining Value to Value Determining Price: It's About Strategy at a System Level," will be held on June 25 from 11:00 AM to 12:00 PM EST. This session will help leaders develop new care pathways and approaches to commercial model innovation using systems thinking: how to develop new storylines of "value" that transition legacy operating models centered on promoting and pushing a product's technical specifications to creating and positioning business for system advantage.

For more information and to register

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June 17 | 8:00AM – 12:30PM EDT
Health Economic Modeling in R: A Hands-On Introduction
Faculty: Felicity Lamrock, PhD, Queen's University Belfast, Belfast, Northern Ireland, UK; Gianluca Baio, PhD, University College London, London, England, UK; Rose Hart, PhD, BresMed, Sheffield, England, UK; Howard Thom, PhD, MSc, University of Bristol, Bristol, England, UK

June 23 | 8:00AM - 12:30PM (SAST)
Budget Impact Analysis: From Theory to Practice
Faculty: Janina de Beer, MEng, Centurion, South Africa; Ilanca Fraser, MPharm, PhD, Centurion, South Africa; Tinashe Mhazo, MSc, Centurion, South Africa; Tienie Stander, MBA, VI Research, Dubai, United Arab Emirates

June 29-30 | 10:00AM – 12:00PM EDT
Risk-Sharing/Performance-Based Arrangements for Drugs and Other Medical Products
Faculty: Louis P. Garrison, PhD, University of Washington, Seattle, WA, USA; Adrian Towse, MA, MPhil, Office of Health Economics, London, England, UK; Josh J. Carlson, MPH, PhD, University of Washington, Seattle, WA, USA

July 13-14 | 10:00AM – 12:00PM EDT
Introduction to Machine Learning Methods
Faculty: Wei-Hsuan Jenny Lo-Ciganic, MSPharm, MS, PhD, University of Florida, Gainesville, FL, USA; Hao Helen Zhang, PhD, University of Arizona, Tucson, AZ, USA; John Seeger, PharmD, DrPH, Optum, Boston, MA, USA

July 20-21 | 8:00AM – 10:00AM EDT
Introduction to Health Technology Assessment
Faculty: Uwe Siebert, MD, MPH, MSc, ScD, UMIT - University for Health Sciences Medical Informatics and Technology, Innsbruck, Austria and Harvard University, Boston, MA, USA; Petra Schnell-Inderst, MPH, PhD, Dipl. Biol, UMIT - University for Health Sciences Medical Informatics and Technology, Innsbruck, Austria

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June 25 | 11:00AM – 12:00PM EDT

From Pricing Determining Value to Value Determining Price: It's About Strategy at a System Level

Guest Speakers:

- Alexander Billioux, MD, DPhil, UnitedHealthcare Government Programs, Baltimore, MD, USA
- Michele Markus, Omnicom Group, New York, NY, USA
- John Singer, Blue Spoon Consulting: Life Sciences, New York, NY, USA

July 15 | 11:00AM – 12:15PM EDT

National Institute for Health and Care Excellence (NICE), UK: Transformation in Action

Guest Speakers:

- Meindert Boysen, PharmD, MSc, NICE, London, England, UK
- Jens Grueger, PhD, Boston Consulting Group, Zurich, Switzerland
- Gillian Leng, CBE, NICE, London, England, UK

September 28 | 11:00AM – 12:30PM EDT

The New Science of Cause and Effect: Causal Revolution Applied

Guest Speakers:

- William H. Crown, PhD, Brandeis University, Waltham, MA, USA
- Judea Pearl, PhD, UCLA, Los Angeles, CA, USA

October 26 | 11:00AM – 12:00PM EDT

Venture Capital Investment: Upstream Decision Making on Value in Healthcare

Guest Speaker:

- Tom Cassels, Rock Health, San Francisco, CA, USA

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October 28	*Sponsored and Presented by* Optum
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EXPANDING THE VALUE CONVERSATION

UNDERSTANDING VALUE IS ESSENTIAL TO MAKING WISE HEALTHCARE DECISIONS. With rising healthcare costs, purchasers want to know how they will benefit from the care they are getting. Today's consumers demand efficiency from everything they purchase and will expect no less from healthcare. The COVID-19 pandemic has stress-tested healthcare systems around the world, called out their weaknesses, and taught us that we need to make better choices. This requires a thorough evaluation of the options, and with its focus on measuring value to improve healthcare decisions, ISPOR is well-positioned to support the necessary changes. In this article, we kick off a series on the definition of healthcare "value" from different stakeholder perspectives. Specifically here, we provide an introductory primer on value with input from interviews with selected experts.

About the Author

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The pandemic offered us a unique opportunity to reimagine healthcare. To make it better, we must first determine what needs to be improved. Value will be an important measure of our success, but it is a complex multidimensional metric. The weights given to different aspects of value vary among individuals and across stakeholder types. Economists think in terms of value for money. "Of course, it depends on perspective and whose value you're talking about," says Peter J. Neumann, ScD, Tufts Medical Center (Boston, MA, USA) and Chair of ISPOR's Special Task Force on Value Frameworks. "What they're willing to pay defines value. From society's perspective there is, of course, the idea of opportunity cost—what are we willing to give up to receive the new service or technology?" However, willingness to pay is difficult to measure in a healthcare system where the ultimate consumers neither pay the price, nor experience the trade-offs.

Merriam-Webster's Dictionary offers a general definition of willingness to pay as "relative worth, utility, or importance."[1] Advertisers often use these terms: the value meal; buy one, get one free; bulk package pricing; and discounted "sale" prices for a limited period. Should we buy more to get the lower unit price? Will we use it all? Should we buy now when we don't need it yet? Will our use justify the price?

At Premera Blue Cross, we explored perceptions of value with focus groups of plan members. Some members associated value with poor quality, a "bargain" whose low price reflects a minimal worth. Value Village, a chain of second-hand thrift stores, was cited as an example. "Cheap" is not the image we want to see attached to healthcare, but when we explained the idea of value for money, none of the interviewees could offer a synonym that adequately captured the concept.

This article provides an overview of the value concept and traditional research methods from the perspective of health economics researchers and health technology assessors. These methods fail to capture the full range of elements that contribute to value. As Neumann notes, "If we know we have an intervention that works, there are broad consequences that we don't usually capture—consequences to the family, society, future investment, science—things like that. Some studies do, but usually the data are not very good and there's a lot of uncertainty around it." Subsequent articles in this series will explore these and other elements of value from the perspectives of stakeholders.

Determining Net Cost

Health economists and policy experts often equate "cost" and "cost-effectiveness". Comparative value is then measured as the incremental cost-effectiveness ratio, which is the incremental net cost (factoring in cost offsets) divided by the improvement in net clinical benefit. The incremental cost-effectiveness ratio measures how much a medical intervention (eg, drug, device, program, surgery) improves health outcomes compared to another intervention or no intervention and whether this justifies the additional dollars spent.

Direct healthcare costs can be predicted with economic models and confirmed by retrospective analysis of large databases, from a payer perspective. Indirect costs are less accessible, but reasonable estimates can usually be made. The societal perspective is commonly used where government is the payer. In the United States, where employers fund a large portion of health insurance, employer perspective modeling is also useful, particularly when evidence suggests an impact on absenteeism, productivity, or longevity in the workforce. Future stakeholder interviews should identify other elements of value. Notwithstanding these different perspectives, incremental net cost can usually be estimated with stakeholder input.

Estimating Benefit: Clinical Perspective

Capturing the net benefit is more challenging. At the core of this, regardless of perspective, is an estimate of the direct clinical benefit to the patient. This includes both positive (eg, improvements in health) and negative (eg, adverse effects or other harms that may result from treatment). Diana I. Brixner, RPh, PhD, Executive Director of the University of Utah's Pharmacotherapy Outcomes Research Center (Salt Lake City, UT, USA) and an expert in large database research, reminds us that to make informed decisions, clinicians need the right comparison. "When a new drug comes to market, the question is always, What incremental benefit does this treatment provide to the standard of care (ie, what I'm paying for today to treat that same disease and that same indication)? And that incremental benefit includes trade-offs. What's the efficacy, safety, route, and frequency of administration? Those are all components of benefit and any one of them may balance another off in the collective average, and—this is the tricky part—an improvement in the patient's quality of life.

> If we know we have an intervention that works, there are broad consequences that we don't usually capture–consequences to the family, society, future investment, science.
>
> – Peter J. Neumann, ScD

"The clear method is to execute a real-world study, collect data from numerous places that are using this product to show that in the real world that is, in fact, true. That's the evidence that managed care wants," said Brixner. Funding will be required to do these studies, and organizations like ISPOR can play a role in that.

Clinical nuance is important, as the University of Michigan's Institute for Healthcare Policy and Innovation's website suggests:

> *Achieving value in healthcare…means ensuring that people receive the medical tests, procedures, and treatments that they need to improve their health—but not services that are unnecessary, nor those whose potential harms or costs outweigh the likely benefits.*[2]
>
> *The concept of clinical nuance…recognizes 2 important facts about the provision of medical care:*
> *(1) medical services differ in the amount of health produced, and*
> *(2) the clinical benefit derived from a medical service depends on who is using it, who is delivering the service, and where it is being delivered.*[3]

Relevant clinical outcomes include longer life, fewer undesirable medical events (heart attack, stroke, fractures, etc), pain relief, and improved function. Organizations including the Institute for Clinical and Economic Review,[4] Memorial Sloan Kettering Cancer Center,[5] the National Comprehensive Cancer Network,[6] and the American Society of Clinical Oncology[7] have developed value frameworks that extend the assessment of benefit to additional domains. These will be addressed later.

Whenever patients interact with the healthcare system, there is risk of unintended harm. Usually the risk is small, compared to the expected benefit, but it must be counted. Along with the more likely possibility of wasted expense when the intervention fails to deliver benefit, this is a good reason to avoid unnecessary care.

The QALY as a Measure of Net Benefit

Despite its widespread use, the quality-adjusted life year (QALY) is acknowledged to be inadequate by most users and vociferously criticized by opponents. The conceptual simplicity of the QALY is both its strength and weakness. QALYs are added by extending an individual's life expectancy, improving the utility assigned to their remaining years, or both. When utility is plotted versus time, the area under the curve with treatment minus the area without treatment represents the net QALY gain. "The cost-per-QALY framework is valuable because it gives us a way to think about this with a common benchmark," says Neumann. "Otherwise, we don't have any standards."

Allowing "experts" to determine the value of a life is ethically and practically problematic.

QALYs are unpopular with the public. Politicians argue that a metric based on life expectancy is weighted against the elderly. Quality adjustment using population-based arbitrary rules to determine utility denies patients self-determination. Desire to continue living is increased by relationships and life milestones but decreased by chronic, poorly controlled pain. In some cases, societal benefit guides resource allocation, as when the Centers for Disease Control and Prevention prioritized vaccinating seniors against COVID-19 to avoid overwhelming hospital intensive care units with patients more likely to have severe disease and causing harm to non-COVID patients.

Patients with disabilities caused by rare diseases are assigned lower utilities. Advocates argue that discounting their lives is discriminatory. Transformative treatments that would allow them to achieve greater independence would likely benefit society as well as improve quality of life. Allowing "experts" to determine the value of a life is ethically and practically problematic. Prioritizing expensive interventions based on quality-adjusted survival might have denied us the brilliant scientific contributions of Stephen Hawking and the work that many other "differently abled" individuals have contributed to make the world a better place.

Payers and those that generate evidence are starting to come together to address what evidence is needed to demonstrate value and then associate reimbursement and coverage to that value.

– Diana I. Brixner, RPh, PhD

Applying population-based utilities to individuals overlooks subjective quality of life. People respond to illness differently, depending on personality, circumstances, and life history. Sudden blindness in an adult may cause extreme anguish and inability to navigate daily life, while an adult born blind has adapted and functions well in most of the same situations. Utility of a given health state would vary among individuals experiencing it and may vary over the lifetime of one individual. Patients with spinal cord injuries typically experience suicidal depression after their injury but can't act on their desire to end life. After adjustment, many of them find fulfillment and some even report a more focused and purposeful life. From this perspective it would be best for the individual patient to assess his/her own utility (experience-based utility value), rather than using population-based preferences,[8-10] but the patient's desire for access to treatment makes it hard for them to be objective.

Recently, ICER has begun reporting equal-value life years gained (evLYG) along with QALYs. Neumann agrees that, "It responds to some of the criticisms that QALYs could discriminate against people that have low baseline health. You can't return them to a higher utility, so it will give you the same utility value as people who are not disabled for the extended length of life." However, he acknowledges, "It doesn't solve the problem altogether because it still has consequences. You don't value certain drugs as much as you would otherwise, given their benefits." Although the evLYG measure does not "discriminate" against cancer patients by designating a year of life with their condition as "worth less" than a year of life for an individual in typical health, it can fail to recognize the full value of medications that improve symptoms for these patients "But do them both," Neumann concludes. "The QALY is one way of doing it. It's not the only way."

Exploring Additional Dimensions of Value in Real-World Evidence

Brixner suggests real-world evidence (RWE) can inform workplace-based metrics important to employers. "One of the big ones is worker productivity. At the end of the day when you look at who is paying the bills, it's the employer. People talk about productivity, absenteeism—all those aspects that need to be quantified for the employer." For the data to be useful, they must come from a credible source. "RWE is the bridge of information between what we have today and what payers are asking for, both public and private." Confirmatory studies, she believes, can address the questions left unanswered by the US Food and Drug Administration's accelerated approval process, and there should be a registry for them as there is for clinical trials. "Payers and those that generate evidence are starting to come together to address what evidence is needed to demonstrate value and then associate reimbursement and coverage to that value."

> Value is a way of thinking through the choices we have to make. When people pretend that there aren't hard choices to be made, that's when bad choices are made.
>
> – Steven D. Pearson, MD, MSc

ICER's value framework is a more holistic approach that adds contextual factors and other considerations that impact value in specific cases. These include ethical considerations, unmet medical need, rare disease status, public health impact, and likelihood of affecting adherence (positively or negatively).[4] ICER President Steven D. Pearson, MD, MSc (Boston, MA, USA) explains the organization's founding vision. "Because I was trained as a doctor, I wanted to improve health. You can improve the health of individual patients and communities, but healthcare is only a part of improving health, and health is only a part of our overall well-being. Value in a healthcare system is how much you can improve that health, realizing that whatever measure we are using, health is not the only object of our health system."

Value assessment is a critical component of the process of improving our healthcare system, particularly when resources are more tightly constrained. "Value is how we use our limited resources to achieve that goal, to improve the health of individual patients and of communities," says Pearson. "It implies that we have to make choices. Value to me is only useful as an idea that forces us to take on the idea of making choices." The pluralistic nature of our healthcare system and decentralized decision making also obscure the choices currently being made. "Our best intention is to do more. Value is a way of thinking through the choices we have to make. When people pretend that there aren't hard choices to be made, that's when bad choices are made."

The Importance of the Patient's Voice

Listening to patients is critical to ICER's review process. "It's reinforced the idea that even we 'smart' doctors don't know what we don't know. We end up making short cuts in the way we think about conditions and people and averages in a complicated world. The more you listen to patients, the more you hear nuance, diversity of experience we never would have guessed—not just diversity in race or income, but the human experience." Patient groups, he says, tend to be more concerned about access. "We need to get a lot better at asking questions, the answers to which would improve our assessments."

ISPOR's Perspective

When ICER and other organizations produced value frameworks, ISPOR convened a Special Task Force to provide guidance for future framework development. The ISPOR initiative produced 7 guidance documents published in 2018.[11-17] One of these identified a longer list of 12 dimensions of value, some of them not included in existing frameworks. Not all of these dimensions are easily quantified, but with stakeholder input they might be included in a multicriteria decision analysis framework. Only 4 of these dimensions (ie, QALYs, net costs, productivity, and adherence-improving factors) had been included in one or more previous frameworks. The other 8 proposed by ISPOR are reduction in uncertainty, risk or fear of contagion, insurance value, severity of disease, value of hope, real option value, equity, and scientific spillovers.[13] Depending on one's perspective, some or all of these may be considered in developing an operational methodology for assessing value in a specific setting.

> The more you listen to patients, the more you hear nuance, diversity of experience we never would have guessed–not just diversity in race or income, but the human experience.
>
> – Steven D. Pearson, MD, MSc

Neumann emphasizes the importance of "better incorporating attitudes toward risk and value to nonpatients when you have a new treatment. If there's a new treatment for Alzheimer's, we're all feeling better about our future—even if we never get Alzheimer's. It's real. You should measure it and understand it. If we're really trying to measure value, we should do it comprehensively."

Next: The Provider Perspective

The concept of value is complex, multidimensional, and varies according to the perspectives of the various stakeholders in our healthcare system. Subsequent articles in this series will include interviews with various stakeholders to explore their understanding of value. As we emerge from the COVID-19 pandemic, we have a unique opportunity to pause, reflect, and create a vision for the future that improves the value delivered and meets the future needs of an expanding society. The next article will present the perspectives of providers and health systems. Later articles will cover the perspectives of payers, plan sponsors (employers), patients, and caregivers.

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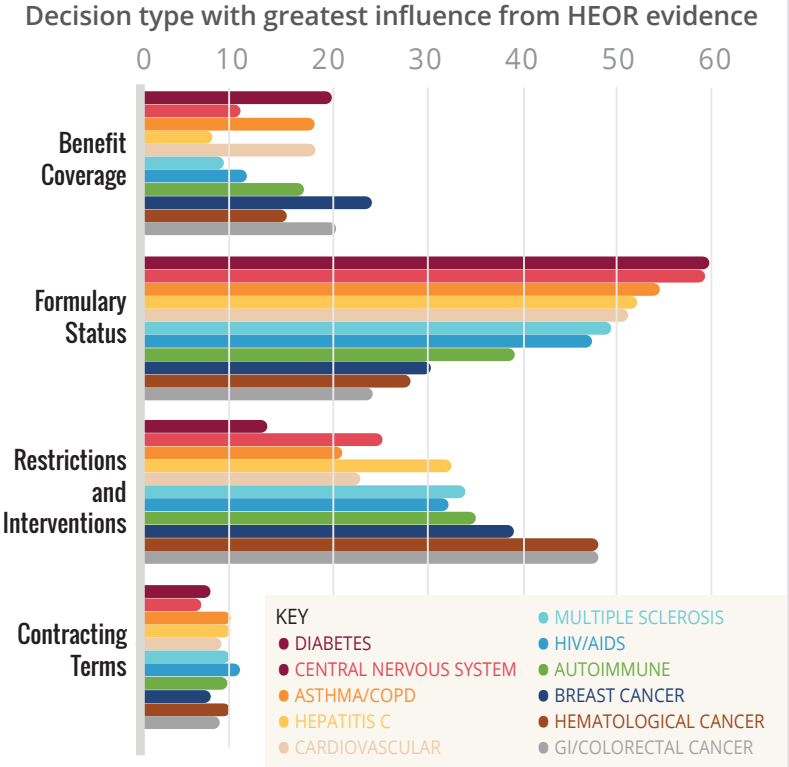
By the Numbers: Healthcare Decision Statistics of Stakeholders for HEOR

Section Editor: **The ISPOR Student Network**
Vasco Miguel Pontinha, Virginia Commonwealth University, Richmond, VA, USA; **Srujitha Marupuru**, University of Arizona, Tucson, AZ, USA; **Enrique Saldarriaga**, University of Washington, Seattle, WA, USA; **Camila Felix Fortis**, Karolinska Institutet, Solna, Sweden; **Ingrid Cox**, University of Tasmania, Australia

4 Aspects to Bridge the Gap Between Health Economics and Outcomes Research and Policy Making[1]

1. *Funders who require the use of scientifically supported interventions* — Drivers of scientific evidence use
2. *National public health agencies as well as other national nonprofit organizations in the public health space* — Supply of scientific evidence
3. *Data on cost-effectiveness of interventions and information at the local level are key to impel stakeholders to act* — Content of evidence
4. *Framing evidence to resonate with different audiences* — Presentation of evidence

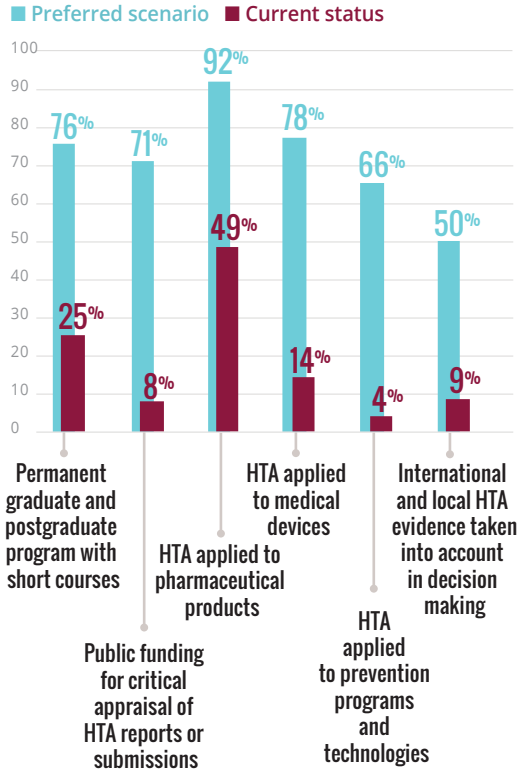
Use of Health Economics and Outcomes Research (HEOR) Evidence in Access Decisions for Pharmacy Benefit Managers and Large Employers



HIV/AIDS indicates human immunodeficiency virus/acquired immunodeficiency syndrome; GI, gastrointestinal; COPD, chronic obstructive pulmonary disease.

Source: Health Strategies Group, Health Economics and Outcomes Research, April 2014

Gaps in Health Technology Assessment (HTA) Implementation Rates Versus Preferred Scenario in the Middle East and North Africa[2]



(Sample comprised of governmental employees)

References available online.

Relevance of the ISPOR Competencies Framework in HEOR Fellowships in the United States

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How relevant is the ISPOR Competencies Framework to HEOR postdoctoral fellows seeking a career in the pharmaceutical industry?

This is the first effort to assess the practical application of the ISPOR Competencies Framework.

The responses of this survey provide insight into the postdoctoral fellow's reception of competencies in shaping fellowship programs and preparing them for careers in HEOR.

ISPOR—The Professional Society for Health Economics and Outcomes Research—has established a set of competencies for health economics and outcomes research (HEOR) professionals. The 41 competencies are organized into 13 topic domains that collectively comprise the ISPOR Health Economics and Outcomes Research Competencies Framework™.[1]

Framing Out the Study

The ISPOR Competencies Framework has great potential to define and support the HEOR discipline. It can have numerous applications, including providing a "roadmap" to prospective candidates applying for HEOR jobs, aligning competencies to specific specialty job tracks within HEOR, and strengthening job postings on sites such as the ISPOR Career Center. This is the first effort to assess the practical application of the ISPOR Competencies Framework.

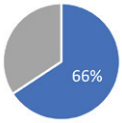
The objective of this study was to assess the relevance and applications of the ISPOR Competencies Framework to post-doctoral fellows seeking a career in the pharmaceutical industry. This was accomplished by asking representative professionals how they were exposed to the competencies within the framework of doing a postdoctoral fellowship in HEOR.

An HEOR Fellow Workgroup, unaffiliated with a professional organization, was established in 2017 to provide a network for PharmD postdoctoral students completing their fellowship in the Northeast region of the United States. Since then, the group has expanded in several ways and now includes more than 100 active members and alumni. Most members have PharmD degrees, but some may have an MPH or PhD in an HEOR-related field and can be in a program from any region in the United States. A short survey of 8 questions was emailed to members and alumni of the HEOR Fellow Workgroup.

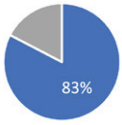
Survey Results

The following demographic data describe the areas of heterogeneity within the sample and show how the Framework can be applied to different subsets of the HEOR workforce, postdoctoral fellows being one type:

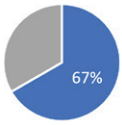
The survey was sent to 60 potential participants; 35 (58%) people responded and were included in the analysis



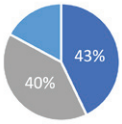
23 (66%) participants were currently in HEOR fellowships, and the remaining proportion had completed their fellowships in the past 3 years



19 (83%) current fellows responded that their fellowships were 18+-month programs



8 (67%) former fellows reported staying in their fellowships longer than 18 months



43% of fellows spent a portion of their time at academic institutions and the rest of their time at pharmaceutical companies, and 40% of fellows spent 100% of their time at pharmaceutical companies

The top 10 competencies in order of relevance were as follows:

1. Teamwork, Team Dynamics, and Relationships
2. Retrospective Claims Database Studies
3. Prospective and Retrospective Observations Studies (Real-World Evidence)

Figure. Excerpts of survey responses.

4. Presentation Development and Delivery
5. Epidemiology, Including Pharmacoepidemiology Studies
6. Health Economic Modeling
7. Systematic Literature Reviews
8. Burden of Illness Analysis
9. Orientation Towards Solutions and Success
10. Statistics and Analytics

The survey included 2 questions about the usefulness of the ISPOR Competencies Framework:

- *"Would HEOR competencies help guide the future fellowship experience?"*
- *"If competencies from the ISPOR Competencies Framework™ were described in HEOR job descriptions, would it help in your future job search process?"*

Some response excerpts are included in the **Figure** to give insight on how programs can use the results of this survey and the ISPOR Competencies Framework.

Building on the Foundation

This research marks the first application of the ISPOR Competencies Framework. The findings will be limited to a specific population of fellowship programs in the United States based on the respondents and certain missing competencies such as outcomes research and patient-reported outcomes, but it demonstrates the power and need for a defined set of competencies in the HEOR profession. The results may vary for international fellows, and it would be worthwhile to expand the sample in a future analysis to include HEOR postdoctoral fellows completing their fellowship outside of the United States.

> This study demonstrates that the ISPOR Competencies Framework is extremely applicable to HEOR fellowships, a postgraduate career opportunity that is increasing in popularity to develop the future leaders of the profession.

The top 10 competencies in the overall group included a mix of methodologic competencies and "soft skills," reflective of new professionals who typically place equal importance on building technical and professional development skills.

The authors believe fellowship programs conducted in the United States may find the results useful in improving the way fellowships are conducted in the future, and build upon existing HEOR fellowship guidelines.[2] This study demonstrates that the ISPOR Competencies Framework is extremely applicable to HEOR fellowships, a postgraduate career opportunity that is increasing in popularity to develop the future leaders of the profession.

Additional analyses were also completed and were presented at the Virtual ISPOR 2021 conference. For information, please contact Soham Shukla (soham.shukla@rutgers.edu).

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Tools for Compensating Patients for Their Patient-Engagement Activities

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There has been little attention paid to identifying best practices in compensating patients for the expertise they provide.

This article describes the development of the first publicly available toolkit that guides compensation decisions.

The toolkit includes a fair-market value calculator with supporting documentation.

Introduction

Patient engagement in health-related research has become a mainstay over the past decade, recognized and promulgated by government, industry, and, of course, patients themselves. The formation of the Patient-Centered Outcomes Research Institute in 2010 has increased interest in patient-centered outcomes research.[1] The value of the patient community's perspective in successful medical product research is also well accepted with the US Food and Drug Administration and other regulators, promoting the engagement of patients and patient groups in all aspects of medical product development.[2-5]

One historical barrier to widespread patient engagement has been disagreement over whether or not to compensate patients for their contributions to patient engagement activities.[6] More recently, there is generally broad agreement that, as experts in their condition, patients should be compensated for the expertise they contribute to drug development for companies. However, stakeholders still lack clarity regarding how, and how much, to compensate for which patient engagement activities.

> The goal was to create a toolbox that would guide compensation of patients and patient groups who are involved in patient engagement activities, mostly related to medical product development.

Fair market value (FMV) calculators are tools that are traditionally used by industry to ensure the compensation rates they are using when engaging doctors, researchers, and other outside experts are both competitive and compliant with regulations. These methods for determining appropriate compensation for clinicians and researchers are not applicable for patients, as many were originally created for healthcare providers, using qualifications only applicable to them. Based on patient group and industry member feedback that an alternative process for determining FMV for patient engagement was needed, the National Health Council, in partnership with Patient-Focused Medicines Development, and guided by 2 advisory committees, developed the first toolbox on compensation for patient engagement activities to support compensation and reimbursement decisions.

How the Toolbox Was Developed

The goal was to create a toolbox that would guide compensation of patients and patient groups who are involved in patient engagement activities, mostly related to medical product development. The toolbox was not meant to be applied to patients involved in clinical trials or in advertising/marketing activities.

Steering and Review Committees

Two committees were formed to support the project work. The Fair Market Value Steering Committee assisted in providing strategic direction and guidance for the project. The steering committee comprised individuals who were knowledgeable about patient engagement and familiar with the compensation of patients, caregivers, and patient-advocacy groups. Throughout the content creation process, the steering committee reviewed the materials and helped to navigate any potential issues that arose in the project. The Fair Market Value Review Committee was dedicated solely to assessing and critically reviewing the content produced, which allowed for a deeper dive into the materials than the steering committee was asked to provide.

Partnerships

The National Healthcare Corporation (NHC) partnered with Patient Focused Medicines Development and the Workgroup of European Cancer Patient Advocacy Networks (WECAN) in tool development. The partners collaborated, shared information, and exchanged deliverables so that the processes and outputs would be efficient and aligned.

Interviews

The NHC team conducted 60 interviews to engage key stakeholders on the topic including, but not limited to, patient advocacy organizations, medical product companies (pharmaceutical, biopharmaceutical, diagnostic, and device), and other research organizations and nonprofits. The NHC also tapped the findings from surveys by the Patient Focused Medicines Development and the Workgroup of European Cancer Patient Advocacy Networks.[7,8]

Wage and Benefits Data

As there is no compensation benchmarking data for "patients," the NHC used compensation benchmarks for positions requiring similar skills, such as hospital patient representatives, and research, marketing, and health education positions. The NHC also used its own 2019 annual compensation survey data to find the appropriate FMV rate for patient organization staff to estimate an hourly consulting rate. Benchmark annual compensation was adjusted to reflect independent consulting services and produce a rate that includes salary, benefits, overhead, and profit based on the market data. This annual compensation was then transformed into an hourly rate by dividing the number of work hours in a typical year.[9,10]

Definitions

It was important that all participants used the same definitions for terminology as we progressed through toolbox development. We used the US Physician Self-Referral ("Stark") Regulation definition in our methodology for this project.[9] We also created a glossary that defined for this project terms, including: individual patient, caregiver, family member, patient group representative, etc.[11] All definitions used in the toolbox can be found here.

Patient Activities Framework

To outline all the patient engagement activities that patients could be involved in, the NHC developed a patient activities framework. To create the framework, the NHC adapted and consolidated an extensive activities list developed by Patient Focused Medicines Development. This document had more than 150 patient engagement activities identified from 20 unique sources.[12] The NHC consolidated the activities into general categories such as cocreation, presentation, mock trial, interview, focus group, reviewer, advisory board member, recruit, etc.[13] The steering and review committees refined it further and added or subtracted categories as appropriate.

> While these tools are currently only available for compensation in the United States, the NHC's partner on this project will soon be adapting the tools for use in Europe.

Reviews and Public Comment Period

The NHC wanted to ensure its membership and the public were able to comment on foundational components of the project, the Compensation Principles and Contracting Principles. The NHC membership and the wider public received notice of the open comment period on the 2 documents in December 2019 with 1 month to submit comments. The 2 documents were refined based on the comments received.

Table. Tools in the toolbox.

Patient Compensation Tools	Patient Contracting Tools
FMV Calculator & supplementary documentation for its use • Patient Activities Framework & Worksheet • User Guide • Methodology • Training Video • Interpreting FMV Results • Interpreting FMV Results • Glossary of Terms	Template Agreements & supplementary documentation for its use • User Guide • Annotated Guide
Compensation Principles	Contracting Principles

Beta Testing of the Calculator

The NHC engaged 11 organizations to beta test the FMV calculator. These organizations included patient advocacy groups, medical product developers, membership organizations, and other research organizations. Once the beta testers returned their feedback via a questionnaire and survey tool, the calculator was further refined and finalized by the steering and review committees. See **Table** for the tools in the toolbox.

FMV Calculator

The purpose of the FMV Calculator is to provide a guide for patient advocates and medical product companies that enter into arrangements where the company is paying a patient or patient advocacy organization for professional services and expenses incurred in connection with the engagement.

The calculator is customizable and allows the user to choose[14]:

- Type of patient (eg, patient, caregiver, family member, patient advocate)
- Skills required for the engagement (eg, newly diagnosed with a specific disease)
- Specific activities the participant will be involved in (eg, input into a protocol)
- Expected time the participants will dedicate to the activity (eg, 1 8-hour day on 3 separate occasions)
- Modifiers that could appropriately alter the rate of compensation (eg, wages lost, the urgency of the work, or potential risks involved)

It should be noted the calculator is a guide only and is expected to be adapted by each user to their own needs. It is not intended to fix compensation rates. A range of rates is provided and the user selects a rate in that range based upon specific circumstances.

Compensation Principles

The Compensation Principles provide guidance on how and when to compensate patients, caregivers, and patient advocacy groups for their involvement in patient engagement activities.

The compensation principles cover the following areas[15]:

- Type of Patient Engagement Participant

- General Compensation
- Administrative/Logistics
- Time Commitment
- Travel and Reimbursement Considerations
- Declining Compensation
- Other Considerations

The principles provided the foundation for the compensation toolbox and guided considerations on such things as what to do when someone declines compensation, or when engaging a celebrity patient, how travel expenses should be reimbursed, and other similar issues.

Contracting Principles and Template Agreements

In collaboration with the Patient Focused Medicines Development and the Workgroup of European Cancer Patient Advocacy Networks, the NHC adapted for use in the United States a set of European-focused legal agreements and contracting principles for interactions between stakeholders and the patient and caregiver community. The Contracting Principles provide guidance on creating agreements between patients and companies for patient engagement activities. The document uses examples to describe concepts like confidential information, intellectual property, data protection, indemnification, adverse event reporting, conflict of interest, and more.[16]

To create template agreements for meaningful partnerships between researchers and members of the patient advocacy community, the NHC adapted templates originally created for a project of the Workgroup of European Cancer Patient Advocacy Networks and the Myeloma Patients Europe that was produced with the Patient Focused Medicines Development and the "independent participation of over 10 pharmaceutical companies."[17] These 4 original template agreements were combined into 1 document and reviewed by a US-based legal team, who updated the documents in alignment with US law. After the template agreements were refined for a US audience, the steering and review committees reviewed them with their own legal and compliance teams and provided recommendations for further updates.

Conclusion and Next Steps

The NHC's online FMV Calculator and other tools can be used to determine compensation for patients, caregivers, and patient groups involved in patient engagement activities taking place between patient organizations and/or individual patients and private companies. Use of the calculator can ensure that patients are fairly compensated and promote consistency across companies. While these tools are currently only available for compensation in the United States, the NHC's partner on this project, the Patient Focused Medicines Development, will soon be adapting the tools for use in Europe.

As a final note, these tools also acknowledge that patients (and caregivers and patient advocates) are experts on the diseases they live with every day and deserve to be compensated as such.

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Fit-for-Purpose Real-World Data Assessments in Oncology: A Call for Cross-Stakeholder Collaboration

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Little information is available regarding fitness for use for most commercially available databases.

The authors have developed a refined real-world evidence database assessment tool.

"Relevance" and "quality" dimensions are combined into a single framework.

Real-world evidence (RWE) remains a promising frontier in evidence generation to support improved health-related patient outcomes. It is defined as evidence derived from analyses of real-world data (RWD) (ie, other than data from controlled clinical trials).[1] RWE thus draws on the complex and diverse landscape of data from medical claims, electronic medical records (EMRs), genomic records, and disease registries, among others. These data sources provide a rich source of information for health economics and outcomes research (HEOR). Some of the potential "use cases" of RWD for HEOR include, for example, determining disease burden and unmet healthcare needs, understanding the standard of care in real-world settings, developing realistic trial designs, studying patient-reported outcomes, and developing cost-effectiveness and budget impact models.

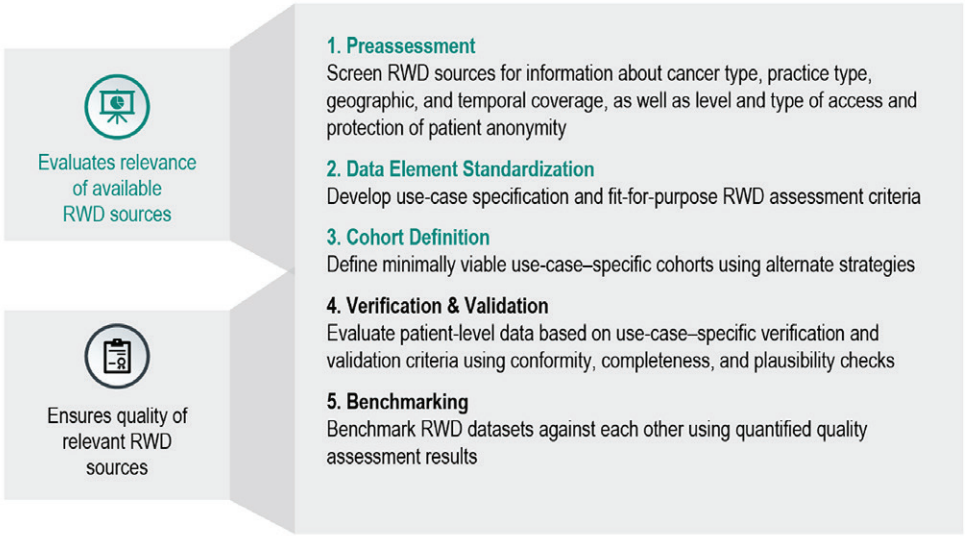
Fit-for-Purpose RWD: The Need for Consensus on Use Case Definitions

Regulatory and payer guidelines have highlighted the importance of "fitness for use," also known as "fitness for purpose," as a key factor that drives the choice of RWD and analytic methods for RWE generation.[1,2] Multiple terminologies have been proposed to define data quality assessment,[3] methods for determining RWD fitness for use,[4] and frameworks for optimizing use of RWE in drug coverage decisions.[5] However, the meaning of fitness for use remains undefined for the full spectrum of RWD use cases in HEOR. There remains a need for clearly outlined "use-case specifications," broadly defined as specifications of RWD requirements and criteria to evaluate RWD fitness for use for specific RWE use cases.

The heterogeneity of data types across different sources of data—and the fragmented data standards among different healthcare institutions and software programs—continue to pose challenges for researchers working with RWD. Indeed, ISPOR's 2021 Science Strategy identifies as its first goal listed under its first theme, *Real-World Evidence,* as "develop[ing] criteria for evaluating the research readiness of real-world databases for HEOR purposes."[6]

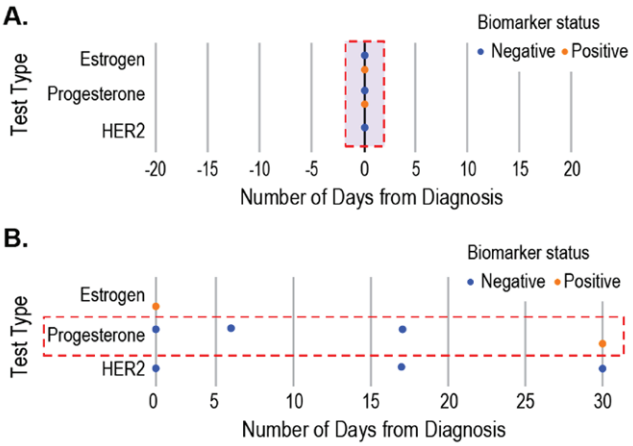
Many entities own and potentially can sell access to (commercialize) real-world

Figure 1. The 5 interlinked iterative steps of the UReQA framework.



RWD indicates real-world data; UReQA, Use-case specific Relevance and Quality Assessment.

Figure 2. Verification (plausibility check) for biomarker status for 2 patients: (A) multiple measurements were recorded on the same day for the same biomarker, with conflicting/unresolved results for patient 1, and; (B) progesterone marker status was negative for 3 measurements, followed by a positive result several days after the third measurement for patient 2.



databases. Currently, databases available for purchase include those from payers (eg, Optum), EMR software providers (eg, McKesson and Flatiron Health), as well as companies that aggregate and link data from multiple sources (eg, IQVIA). Academic institutions and private entities with access to in-house data also may own their data and collaborate with outside researchers (eg, Kaiser Permanente Center for Health Research). A key challenge in working with real-world datasets is to determine which databases are appropriate for purchase in order to support specific research needs. In our experience, little information is available regarding fitness for use of most commercially available datasets.

Combining Relevance and Quality Assessments for RWD Selection: The UReQA Framework

We have developed and refined a real-world database assessment tool named the Use-case specific Relevance and Quality Assessment (UReQA) framework, described in our poster presented at Virtual ISPOR 2021.[7] The framework was developed for evaluation of commercial database offerings in the United States and is based on learnings from quality assessments to support retrospective outcomes studies in oncology. Our aim was to combine the "relevance" and "quality" dimensions of RWD assessment into a single framework to inform the choice of fit-for-purpose RWD to address specific scientific questions. The UReQA framework consists of 5 connected, iterative steps, beginning with (1) a preassessment step using a standard questionnaire for database providers to present high-level information about oncology-specific characteristics of the database, such as cancer type, practice type, and geographic and temporal coverage (**Figure 1**).[7] For databases determined by preassessment to meet use case requirements, the subsequent steps in the framework are then applied to assess the database relevance and quality in more detail.

The next step in the framework is (2) data element standardization, which entails developing use-case specification and assessment criteria appropriate for the research plan. The core components of a use-case specification include the following:

(a) A list of key data elements needed for the study

(b) For each key data element, the variable definitions, constraints, and formats (collectively termed "business rules")

(c) A list of quality checks that establish internal and external validity for key data elements, and

(d) Clearly identified, use-case–specific quality thresholds for validation and benchmarking

The subsequent steps in the framework are applied in interlinked and iterative fashion as follows:

(3) Use of alternative strategies to define use-case–specific study cohorts

(4) Verification and validation of patient-level data against the list of prespecified quality checks, and

(5) Benchmarking real-world datasets for fit-for-purpose use in context of specific use cases

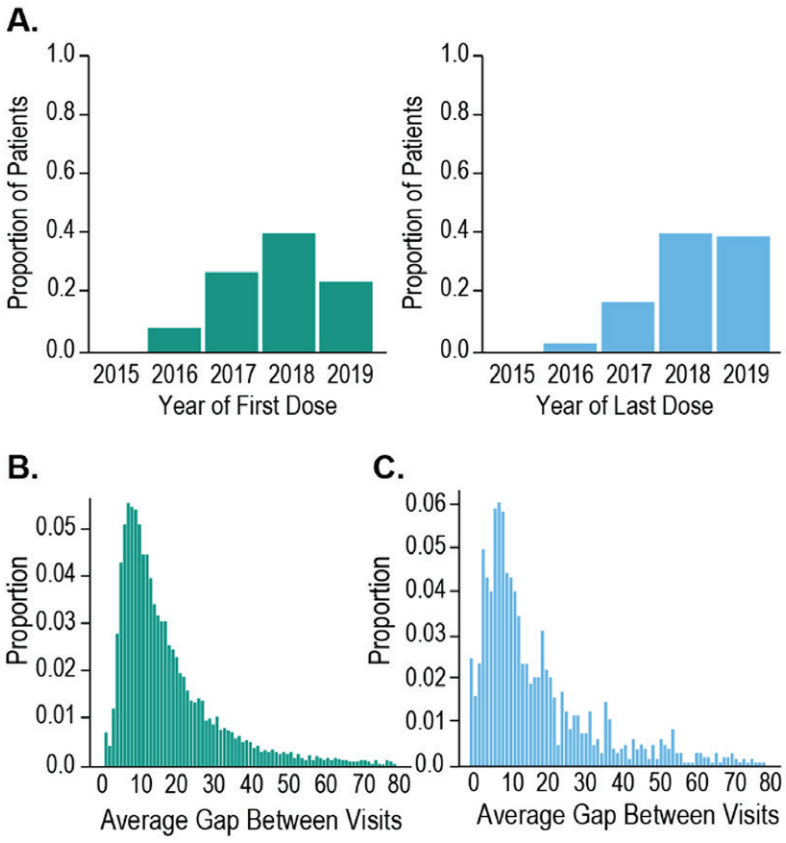
A use-case specification, therefore, outlines a blueprint for fit-for-purpose evaluation of RWD and may form the basis for agreement on quality assessment and reporting requirements across all relevant stakeholders.

An Example of UReQA Framework Application: Real-World Time-to-Treatment Discontinuation

We illustrate the application of UReQA framework steps 2 through 5 by evaluating 2 datasets comprising anonymized EMR data of patients with advanced cancer, cohorts A and B, for estimating an established surrogate effectiveness endpoint for real-world oncology studies: namely, real-world time-to-treatment discontinuation (rwTTD), defined as the time from the start of a systemic anticancer therapy to the time of discontinuation of that therapy for any reason, including death.[7-9] The TTD for continuously administered anticancer medications in randomized controlled trials has been associated with overall survival and with the length of time from drug initiation to disease progression or death. It is calculated as the [(date of last recorded dose – date of first recorded dose) + 1 day] for the agent or regimen of interest within a specific setting or line of therapy.

Key data elements required to estimate rwTTD include records of anticancer treatments administered, clinical visit dates, and mortality, in addition to biomarker testing results to define cancer type. The definitions of cohorts A and B involved stratification using biomarker test results, which in turn required unambiguous determination of biomarker status at specific timepoints with regard to rwTTD estimation. We plotted temporal trends in biomarker testing results as a key data element required for use-case specification and, as a verification check, discovered co-occurring (on the same day) and conflicting/unresolved biomarker results, illustrated for 2 patients in **Figure 2**.[7] Validation checks for data completeness found an unexpected reduction in annual frequency of treatment initiation and treatment discontinuation, highlighting possible incompleteness or discrepancy among treatment records (**Figure 3A**), in addition to differences in the average gap identified between visits as compared with a

Figure 3. Validation (completeness checks): (A) unexpected reduction found in annual frequency of treatment initiation and treatment discontinuation for cohort A, highlighting possible incompleteness of treatment records, and differences in average gap identified between visits in (B) cohort A and (C) cohort B as compared with reference benchmark. The check was implemented using the same criteria for the 2 different real-world data sources.



	Days Between Visits		
	Mean (SD)	Median (IQR)	Range
Cohort A (structured EMR); N=16,406	26 (52)	14 (8–26)	0–2,436
Cohort B (structured EMR); N=982	27 (51)	13 (7–27)	0–945
Benchmark (structured + unstructured EMR)	13 (17)	10 (6–15)	0–733

IQR, interquartile range

EMR indicates electronic medical records;
IQR indicates interquartile range.

Table. Plausibility/completeness check of mortality records: decreasing trend identified in percentage mortality with increasing age group in cohorts A and B. The check was implemented using the same criteria for the 2 different real-world data sources.

	Cohort A		Cohort B	
Age, years	N	Died, N (%)	N	Died, N (%)
≤64	8132	3842 (47)	473	318 (67)
65–74	5369	2432 (45)	326	195 (60)
75–84	2397	1047 (44)	143	77 (54)
≥85	192	72 (38)	8	2 (25)
Missing	330	164 (50)	38	17 (45)
Total	16,420	7557 (46)	988	609 (62)

reference benchmark (**Figures 3B, 3C**). A further validation check examining the completeness of mortality event records identified a decreasing trend in percentage mortality with increasing age group (**Table**).[7] Thus, in our example, fit-for-purpose RWD assessment revealed important insights into the nature of the 2 RWD sources, with varied levels of potential impact on estimation of the rwTTD use case.

A Call for Cross-Stakeholder Collaboration

We believe that a cross-stakeholder collaboration is required to arrive at a shared definition of use-case specifications, including relevant quality thresholds and identification of benchmarking resources for validation strategies. Iterative evolution of use-case–specific requirements, training for increased awareness of application methods, standardization of fit-for-purpose quality reporting, and transparency of findings are foundational capabilities to build a robust and reliable RWD ecosystem.

A shared definition of fitness for purpose will benefit all stakeholders. For health technology assessment (HTA) and regulatory decision makers, a shared definition would outline expectations in the form of reliability and quality requirements associated with specific uses of RWD. For sponsors and pharma, a shared definition of fitness for purpose would enable proactive mapping between available RWD and specific use cases, leading to more efficient identification of data gaps and improved engagement of data providers. For data providers, a well-defined use-case specification could drive the data extraction and curation pipeline as well as inform validation strategies for automated components of the data delivery pipeline. For physicians and patients, a well-defined specification for secondary use of healthcare data may help prioritize specific key data elements for EMR implementation, yield reliable RWE for clinical decision making, and minimize inefficiencies resulting from less-than-optimal evidence generation in support of patient care.

Concluding Thoughts

Ongoing efforts related to RWD transparency,[10] terminologies, and

protocols to assess data,[3,4] as well as reporting templates (eg, STaRT-RWE[11]), are likely to require an agreement on fitness-for-use requirements and quality assessment criteria for RWD among relevant stakeholders. A relevance assessment framework is likely to drive benefits for all stakeholders involved in the specification development and maintenance effort.

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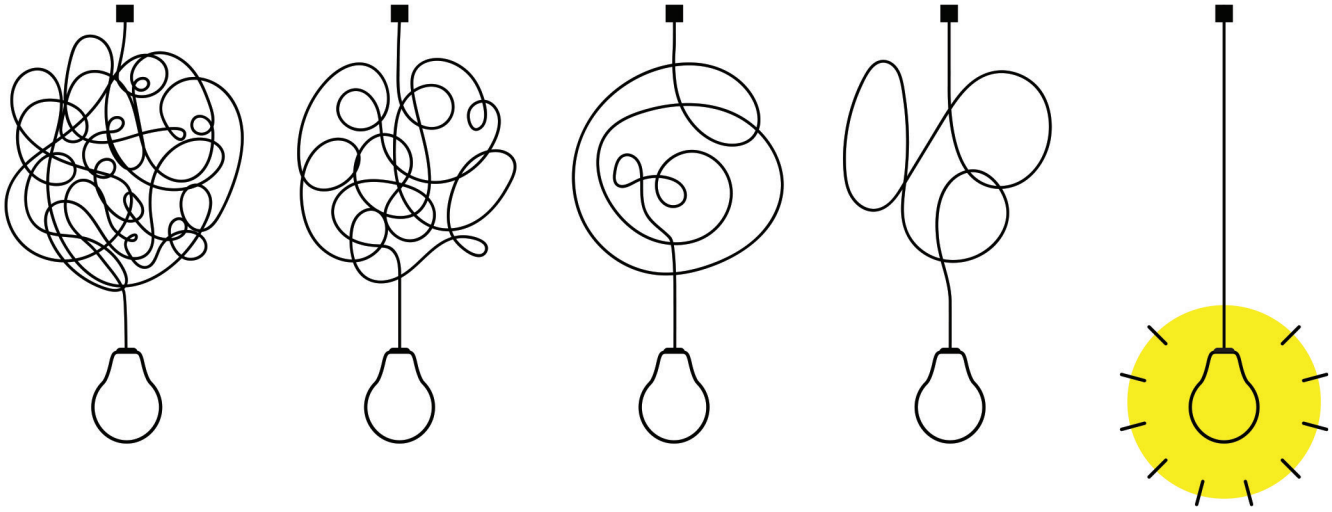

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