NOVEMBER/DECEMBER 2019 VOL. 5, NO. 6

VALUE & OUTCOMES SPOTLIGHT

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VALUE & OUTCOMES
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NOVEMBER/DECEMBER 2019
VOL. 5, NO. 6

TABLE OF CONTENTS

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.

ISPOR
Improving healthcare decisions

VALUE & OUTCOMES SPOTLIGHT
PUBLISHING, SUBSCRIPTION, AND ADVERTISING OFFICE:

Value & Outcomes Spotlight
Print: ISSN 2375-866X
Online: ISSN 2375-8678
USPS: 019121

Published bi-monthly by:
ISPOR
505 Lawrence Square Blvd, S
Lawrenceville, NJ 08648 USA

Periodicals Postage paid at
Annapolis, MD 21401
and at additional mailing offices.

POSTMASTER: Send address changes to:
Value & Outcomes Spotlight
505 Lawrence Square Blvd, S
Lawrenceville, NJ 08648 USA

FROM THE EDITOR

Among a host of challenges facing healthcare delivery and financing systems around the world, figuring out how to balance value, access, and affordability in an era of unprecedented medical innovation stands apart as critical. Media headlines touting the latest life-saving intervention or disease cure now seem commonplace, and this is all great news until we see the subhead expressing payer concerns for the 6-figure price tag. How are financially strained health systems supposed to provide reimbursement coverage for such interventions? How can patients be expected to reconcile the elation of hearing about a cure with the despair of being told that access is in question? And are the traditional tools and techniques of health economics and technology assessment up to the challenge? So many difficult questions…

Our Society sits at the very nexus of these questions and is not shying away from the controversy. ISPOR's initiative on Value Assessment Frameworks has released seven Task Force Reports and held a summit specifically devoted to these frameworks, while key publications in ISPOR's flagship journal, *Value in Health*, have tackled the issue of affordability in economic evaluation. Now it's our turn to address these questions. The feature article in this issue of *Value & Outcomes Spotlight* highlights new thinking regarding the concept of value, problems with traditional cost-effectiveness thresholds, and the promise of value-based insurance design. Another article summarizes a panel discussion from the ISPOR Warsaw regional conference earlier this year devoted to the potential for managed entry agreements to alleviate the budgetary impact of innovative oncology treatments. We have a by-the-numbers infographic and, to cap things off, our Q&A section features a representative of Humana, who describes their approach to value-based care.

In addition to the value-themed content, we include a variety of material of relevance to our Society. An HEOR article makes a plea for open-source economic models and another questions whether—as real-world data sources and analytic methods continue to improve—we even need randomized controlled trials for medical devices any longer. Our ISPOR Central section features a profile of Jo Mauskopf PhD, who we congratulate for this year's Marilyn Dix Smith Leadership Award. Finally, we include a photo gallery from the ISPOR Europe 2019 meeting, which recently took place in Copenhagen, and we highlight abstract submission deadlines and other planning items for ISPOR's conferences and meetings in 2020.

All of us here at *Value & Outcomes Spotlight* wish you the best for the holiday season and new year. See you in 2020!

David Thompson, PhD
Editor-in-Chief,
Value & Outcomes Spotlight

ISPOR SPEAKS

Transparency in Real-World Evidence: Trust, but Verify

Lucinda Orsini, DPM, MPH, Associate Chief Science Officer, ISPOR

As healthcare decision-making complexity continues to intensify, health economics and outcomes research methods and experts have never been in higher demand. Innovative treatments with curative potential based on precision/personalized medicine have become a reality. The digital revolution is quickly coming to healthcare, including artificial intelligence algorithms aiding radiologists in diagnosing patients or augmented reality in the operating suite. However, these cutting-edge technologies complicate the value-determination process of patients, payers, and society, and accordingly, the healthcare budget-planning process. The increasingly complex innovative treatment options, combined with the growing focus on equity and access to healthcare, present a challenging combination of issues for decision makers.

In order to address these healthcare challenges, data are becoming the new "coin of the realm." While not a panacea, there is hope that understanding the nuances of healthcare delivery (ie, what is working and what isn't) will lead to a feedback loop of information that can make a functioning learning healthcare system a reality. Only by understanding what was done, why it was done, and the resultant outcome can we move closer to value-based healthcare.

There is growing interest in the use of "real-world" data (RWD) and their derivations into real-world evidence (RWE) to help inform healthcare decisions. With the advent of 21st Century Cures' mandate for the US Food and Drug Administration (FDA) to consider how to use RWE in regulatory decision making, RWD is expanding beyond signal detection and safety monitoring to contributing to treatment efficacy/effectiveness decision making. While payers may have been using postapproval observational data for coverage and reimbursement support and forward-looking single-payer systems and closed healthcare catchments like Kaiser Permanente are using RWE to drive improvements in healthcare delivery and quality, the regulatory use-cases are now driving RWE to a new plane in decision making.

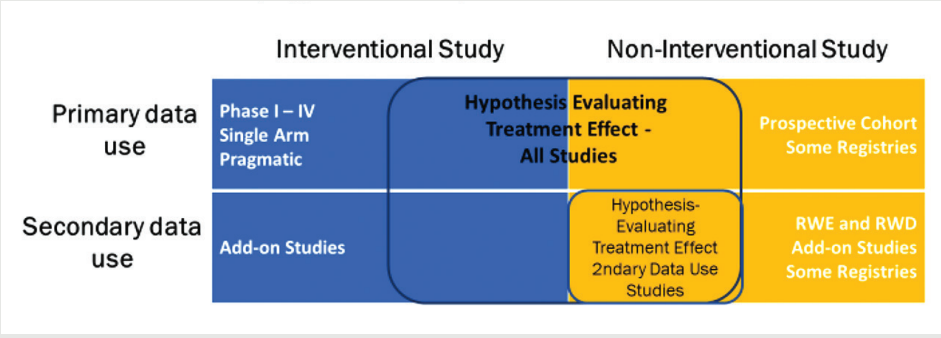
This creates urgency to develop mechanisms that promote trust in the evidence-generation process and enable decision makers to evaluate the quality of the methods and resulting evidence from RWE studies.[1-5] In other sectors such as government and consumer markets, transparency is a critical tool to engender trust across stakeholders and to enable the judgement of the quality of information being exchanged. It is intended to aid decision makers to set priorities and reach conclusions that are legitimate and fair—and perceived as such.[6] In evidence-based medicine, these needs are similar. Regulatory, coverage and reimbursement, and other healthcare decision makers need to be able to evaluate and make informed decisions based on high-quality, relevant evidence.

The need for increasing credibility in RWE is becoming more important as studies are being performed for purposes of informing healthcare decisions with more acceptance and impact. This is especially relevant as access to underlying data is increasingly difficult due to distrusted data networks and privacy laws, and as more studies are being performed with multiple underlying databases or within the "black box" of a machine learning algorithm.

Study registration—particularly for hypothesis-evaluating treatment effectiveness (HETE) studies—has been proposed as an important mechanism for improving transparency and trust. However, existing study registries such as ENCePP/EU-PAS and ClinicalTrials.gov are either oriented toward studies involving primary data collection, such as (randomized) controlled trials or prospective observational studies, or they lack many of the features that should be incorporated in a study registry system designed to improve transparency and trust for studies performed on existing data, often referred to as secondary data use (Figure 1).[7]

Building on the heritage of ISPOR's joint task force on RWE with the International Society of Pharmacoepidemiology

Figure 1. Data Use and Study Type Relationship Schematic



(ISPE), which identified posting a HETE study protocol and analysis plan on a public study registration site prior to conducting the study analysis as a key recommendation,[8] ISPOR has been leading the transparency charge. With our other high touch partners—ISPE, the Duke-Margolis Center for Health Policy, and the National Pharmaceutical Council—we've produced a white paper discussing the need for and recommendations for building a culture of transparency in RWE development and reporting. This effort starts with recommendations to modify or create a study registry site that may be fit-for-purpose for secondary data-use studies focused on causal inference (eg, HETE studies).

Near term, identifying the most suitable location or repository option(s) for preregistration of HETE RWE studies, with special considerations for non-interventional research, is paramount. Using one of the existing platforms (specifically leveraging the experience, expertise, and resources already allocated to these programs) is the most expeditious path forward. While current registry sites are not perfect for this purpose, they are good enough for RWE researchers to begin using them now as other longer-term options are evaluated and defined, including the opportunity to build a new registry.

In the medium term, determinations on additional modifications needed and how workload is affected are key to ensuring long-term success. Efforts will begin in parallel to near-term actions to determine what variables and documents should be registered and when. The starting point is surveying RWE researchers on what they feel is needed, including options for an embargo process, and how we might streamline pain points. The initiative will also work with other external efforts to capitalize on related workstreams, such as those looking at structured reporting and protocol templates that can inform data collection elements needed in a registry site. Definitions of prelooking and wording around attestation will need to be created and evaluated, as well as user reports and key performance indicators. Pilot testing of the mock-up site with actual research projects will be the culmination of mid-term objectives.

The long-term intention is to make registration of certain HETE RWE studies routine in the same way that clinical trials are now registered. Specifically, this is seen to involve studies intended for regulatory, payer, or other healthcare decision making, including peer-reviewed publications. The benefit of routine registration is to get closer to a full understanding of the totality of planned and completed HETE RWE research.

Other considerations also have to be taken into account, including the understanding that transparency does not equal quality—it only allows the end users of the research the best possible chance at making their own determination about how relevant and robust the results may be to inform the question at hand. The idea of what constitutes an appropriate or inappropriate amount of prelooking at the dataset prior to study start will also need to be addressed. While our initial thinking is to be "nonjudgmental" in defining levels of prelooking—only requiring transparency about what was done and for what purpose—the practicalities of that thinking will need to be tested. Versioning of study documents, including protocols and analysis plans, will also need to be defined at least loosely: What amount of change would require an updated document? How many versions are too many? and Does timing of the version lead to suspect results? Finally, incentivizing use of the registry is something that we will have to bear in mind; often such efforts require some motivating factor in order to become standard practice. Whether it's requirement by decision making end users (eg, FDA, EMA [European Medicines Agency], journal editors, or health technology assessment bodies) or incentives (eg, faster-track publication or seal of approval), we need to make sure that the evaluators of these studies are closely aligned with this initiative.

We've encountered a groundswell of multistakeholder support for this effort to date through our comments on the white paper, at the ISPOR Scientific Summit in October in Baltimore, and in the sessions at the latest ISPOR European meeting in Copenhagen in November. While we continue to work on the details with our steering committee and partners, it seems clear that we need to pursue a path forward as expeditiously as possible, but only with the combined efforts of the affected stakeholders, researchers, and the end users. As the potential use of RWE to support decision making for market authorization, reimbursement, and clinical guideline development grows, the need to trust that evidence grows correspondingly. Improving the culture of transparency can help shine light on study practices so that these end users of the results are able to make a better determination about study quality for themselves. •

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HEOR NEWS

A diverse collection of news briefs from the global HEOR community.

1 Administering Specialty Drugs Outside Hospitals Can Improve Care and Reduce Costs by $4 Billion Each Year

(United Health Group)

A brief issued by United Health Group says administering specialty drugs in physicians' offices and patients' homes instead of hospitals "reduces the cost of the drugs and their administration by $16,000 to $37,000 per privately insured patient per year for 5 conditions that account for over 75% of spending on administered drugs." The conditions examined are multiple sclerosis, immune deficiency, rheumatoid arthritis, inflammatory bowel disease, and cancer chemotherapy.

https://tinyurl.com/yyj8l5zt

2 Sharing Anonymized Patient-Level Data Where There Is a Mixed Public and Private Benefit: A New Report

(NHS Health Research Authority)

Research from the Health Research Authority and the University of Sheffield shows that patients aren't always against their data being used by commercial organizations, if they can be shown how that data can be used to develop healthcare products and services.

https://tinyurl.com/y5vxa26f

3 Google, Mayo Clinic Strike Sweeping Partnership on Patient Data (STAT)

Mayo Clinic announced in September that it has struck a sweeping partnership with Google to store patient data in the cloud and build products using artificial intelligence and other technologies to improve care.

https://tinyurl.com/y6bnzn5f

4 A Scoping Review on the Roles and Tasks of Peer Reviewers in the Manuscript Review Process in Biomedical Journals *(BMC Medicine)*

Although peer reviewers are important to the manuscript review process, their roles and tasks are poorly defined, and a scoping review suggests that not overburdening these key people could result in better peer review.

https://tinyurl.com/y69p7wmx

5 Closing Gaps in Real-World Evidence Through Data Linkage

Kevin Haynes, principal scientist at HealthCore-NERI, spoke with HealthEconomics.com to discuss about how the fragmentation of patient care in the US healthcare system leads to fragmented data, and how to close gaps in real-world evidence through data linkage.

https://tinyurl.com/y2k5qezg

6 Pelosi's Drug Pricing Plan Is More Aggressive Than Expected (STAT)

STAT reports that Nancy Pelosi's drug pricing plan is "dramatically" more aggressive than expected, after viewing copies of the plan shared by lobbyists. Among other things, the plan allows the federal government to negotiate the price of 250 medicines and forces drug makers to offer those prices commercially.

https://tinyurl.com/y4hllray

7 Cigna Rolls Out New Plan to Fully Cover Multimillion-Dollar Gene Therapies (Reuters)

In September, Cigna introduced a plan that the insurer claims will fully cover expensive gene therapies and eliminate any out-of-pocket payments for customers. The first 2 approved gene therapies, Luxturna and Zolgensma, are included in the plan.

https://tinyurl.com/y6drcc5q

8 ICER to Assess Treatments for Cystic Fibrosis (ICER)

ICER will assess the comparative clinical effectiveness and value of therapies for cystic fibrosis. The report will focus on Vertex Pharmaceuticals' elexacaftor/tezacaftor/ivacaftor, which has a PDUFA date of March 19, 2020. ICER also will examine any new data that have become available since its May 2018 review of 3 other cystic fibrosis treatments already approved by the US Food and Drug Administration: Vertex's Symdeko, Orkambi, and Kalydeco.

https://tinyurl.com/y4j9cd84

9 Novo Nordisk Offers Programs to Lower Insulin Costs as Pressure Over Pricing Mounts (Pharmalot)

Novo Nordisk announced in September 2 programs that are designed to mitigate rising costs for patients. The effort involves a $99 cash card that can be used by anyone—regardless of whether they have insurance coverage—for a month's supply and the introduction of authorized generic versions of 2 different insulin products at half the list price.

https://tinyurl.com/y6ts5anw

10 Will Gavin Newsom's Plan Lower Prescription Drug Costs in California? (San Francisco Chronicle)

On August 22, the Department of Healthcare Services, which administers California's Medi-Cal program, began to solicit proposals from companies to help the state administer its pharmacy benefits. The transition is expected to be completed by 2021.

https://tinyurl.com/y3c92344

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ISPOR Europe 2019 | Copenhagen, Denmark

TRANSFORMATIVE.

Right: Full house at ISPOR plenary session.

Above: Poster discussion with authors.

SHARING

Right: ISPOR President Nancy J. Devlin, PhD.

Above: Evening networking reception in the poster and exhibit hall.

Right: Attendees line up for professional headshots at the onsite studio sponsored by Evidera.

CHANGING PERSPECTIVES.

Above: Plenary speakers (from left to right), Bogi Eliasen (moderator), Julian Isla, Alexandra Goncalves, Elena Bonfiglioli, Peter Knox, Ernst Kuipers, and Rebecca Miksad.

Photo credit: Christian Dusek Photography

Below: Plenary speakers (from left to right), Petra Wilson (moderator), Suzanne Schrandt, and Pekka Kahri.

Below: Huron Life Sciences' HEOR Theater event in the poster and exhibit hall.

INSIGHTS.

(AND UNQUESTIONABLY A WHOLE LOT OF FUN.)

Clockwise from top left: Members using selfie frame at the ISPOR booth. Members posing for a group shot. Members literally jumping for joy from being a part of ISPOR Europe 2019.

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FROM THE JOURNALS

Section Editors:
Soraya Azmi, MBBS, MPH, Veras Research, Selangor, Malaysia; **Agnes Benedict, MSc, MA**, Evidera, Budapest, Hungary

In our "From the Journals" section, we highlight an article from a recently published issue of either *Value in Health* or *Value in Health Regional Issues* that we hope you find informative and relevant.

Value in Health Regional Issues. 2019;19: 122-131.

External Reference Pricing for Pharmaceuticals: A Survey and Literature Review to Describe Best Practices for Countries With Expanding Healthcare Coverage

Anke-Peggy Holtorf, Fotini Gialama, Kalman Emry Wijaya, Zoltan Kalo

External reference pricing (ERP) is defined as a price policy whereby a government compares the price of a medicine to one or several other countries to derive a price in their own country or context. The method has been used as a price regulation tool for cost containment and to ensure that a country (or payer organization) does not pay an unreasonable price compared to other comparator countries. First introduced in Europe, the practice is now widely used, including in recent years, by countries that are newly entering the fold, which are described by the authors as countries with expanding healthcare coverage. This article by Holtorf et al provides interesting insight into the use of this method among countries, particularly in countries with expanding healthcare coverage. Holtorf et al aimed to describe best practices in this area based on past experiences and current policies being implemented.

The study utilized literature review and survey methods. As part of literature review, the authors gathered both scientific and gray literature using specific search terms. The survey included pharmaceutical market access professionals from Abbott and from 17 countries with expanding healthcare coverage in Asia (Pakistan, Kazakhstan), the Middle East (11 countries) as well as Russia, Ukraine, and South Africa. In order to gain insight into Latin America, which was not covered by the survey, the authors utilized summary referencing information from commercial pricing data services. The authors found few publications that related to ERP in the countries with expanding healthcare coverage, and hence, the survey provided information to supplement understanding about processes in those countries. The authors described their key results divided into features of ERP within mature healthcare coverage systems (such as in Europe) and features of ERP systems in countries with expanding healthcare coverage and highlighted their differences. These differences in mature healthcare countries were in (i) **the scope of the products** (ie, countries with expanding healthcare coverage applied ERP to a broad range of products as opposed to innovative on-patent products); (ii) **the stage in life-cycle of the products** (eg, by the time an innovative product reaches the country with expanding healthcare coverage, the product may have already have been on the market for many years, which changes the value framework used earlier); (iii) **source of price information** (ie, countries with expanding healthcare coverage rely on information from the manufacturer or distributor and therefore lack a wider perspective); and (iv) **definition of price** (eg, when these are not well-defined, the price comparisons would be less robust). The review revealed that the impact of ERP is mixed, with reviewed articles tending to argue that ERP will result in some reduction in price but there is scarce evidence of long-run effects on prices, access, availability, quality, and healthcare.

As part of an analysis of their findings, the authors provide a set of recommendations for the use of ERP as a national pricing policy. These were categorized to directly relate to ERP and general recommendations for pricing policies and listed in 12 main points. As a very brief summary, these were: (i) that the scope of ERP should focus on on-patent drugs; (ii) the basket of comparators should be limited to 5 to 7 countries with similar local environments; (iii) the definition of price should be ex-factory price free of markups, taxes, discounts or rebates; (iv) there should be a contingency plan for temporary distortions like currency rate changes; (v) source of price information should be from a combination of sources nationally and internationally; (vi) price calculation should be the average or median price of the same product; (vii) prevent exchange rate volatility by applying a moving exchange rate or use a purchasing power parity exchange rate; (viii) price revisions should not be more than annual or biannual; (ix) for incomplete data, determine temporary prices based on best available evidence; (x) enforcement should be based on clear rules for appeal to prevent shortages; (xi) a need to monitor and evaluate effects on price policies; and (xii) ERP should be part of a comprehensive pharmaceutical policy, along with reimbursement and consumption of pharmaceuticals.

This paper would be of interest to many of our readers since there is limited evidence on this topic in countries with expanding healthcare coverage. Readers who are a part of the evaluating agencies within governments—especially those who are in countries with expanding healthcare coverage—would benefit from the paper's insights, and so would pharmaceutical industry readers who are looking to expand into the markets described. Researchers and other readers would also find the article enlightening and helpful by providing an understanding of the context to the decision-making process in different regions.

AWARDS

Pioneer and Mentor: Jo Mauskopf Recognized for Her Long-Time Leadership in ISPOR and in the Field of HEOR

If it wasn't for lab animals, **Josephine Mauskopf, PhD, MHA**, ISPOR's 2019 Marilyn Dix Smith Leadership Award winner, may never have found her way into health economics research, where she stands as an extremely soft-spoken giant in the field.

After achieving her master's in pharmacology and physiology at Duke University, Mauskopf took some time off to have her children, and then went back to work as a lab technician. "But basically, I didn't like killing the animals. I decided I couldn't be a theoretical physiologist and went back to school."

While at Duke getting her master's in health administration, "they decided they needed someone to help teach health economics, so they said they'd pay for me to go to school and get a PhD in economics." After working for a couple of years at Duke, where she remains, Mauskopf came to RTI-HS, where she is vice president of health economics. "With one or two breaks, I've been at RTI ever since."

A Pioneer in the Field

When Mauskopf started working at RTI, it was 1983, and Ronald Reagan was president. Under his administration, the rule was put into place that every regulation had to have a cost-benefit analysis performed. "It opened up a lot of research opportunities and RTI had people who could do the cost side of it, but they were looking for someone to estimate the health benefits for environmental and food safety regulations," Mauskopf says. "This was a perfect job for me because it was doing economic analyses, but using my health background as well."

At first, she was doing work for the Environmental Protection Agency and the Occupational Safety and Health Administration, looking at asbestos and hazardous waste regulations. "And then they set up a new group in FDA, the Center for Food Safety and Applied Nutrition, and I won a contract to do some work for them estimating the benefits of food safety and food labeling regulations," she says. "That was quite exciting because they wanted something fairly simple, and that's when I started getting into the literature that I use for the pharmaceutical work." For US Food and Drug Administration (FDA), Mauskopf created a cost-effectiveness model measuring the value of avoiding any food-borne illness, in terms of quality-adjusted life years, a model she believes FDA continued to use for many years after she stopped doing this type of work.

Around the same time Burroughs Wellcome (which later became GlaxoSmithKline) was developing AZT (azidothymidine) for HIV infection, and she received some work from the company doing economic analyses for that drug and others. This led to a job as department head of Economics Research at Burroughs Wellcome and later, director of Pharmacoeconomics Research for Anti-Virals and Anti-Infectives at Glaxo Wellcome Inc. She stayed at the company for 4 and a half years.

According to Mauskopf, being on the industry side "was really helpful, because doing studies while not really understanding the drug development process was a bit tricky." Not long after Wellcome was taken over by Glaxo, RTI asked Mauskopf to return and set up a group that would focus on pharmaceutical industry studies.

Getting Involved with ISPOR and Budget Impact Analysis

It was while Mauskopf was at Burroughs Wellcome that ISPOR formed. "Actually, I was not invited to be a founding member of it; I was a bit upset by that," she says. "But my boss, Hugh Tilson, was invited to be a founding member and paid for me to go to the first meeting. And that's when I started to get involved. I went to an organizational meeting about *Value in Health* at the first or second conference, and I became a co-editor of *Value in Health* with Joel Hay; and when he resigned, I became editor-in-chief." She was editor-in-chief of the journal from 2002 to 2010.

Josephine Mauskopf pictured with Federico Augustovski at ISPOR 2019.

In the early days of ISPOR, National Institute for Health and Care Excellence was being set up in the United Kingdom, and Mauskopf became interested in measuring the budget impact of medical interventions. "I wrote a paper that was published in *Value in Health*, figuring out how you could use the same Markov model for cost-effectiveness and budget-impact analyses, for a new intervention by a simple change in the programming of the Markov model." She emphasizes that she developed that on her own time, not for any client. The Academy of Managed Care Pharmacy was also developing its own guidelines at the time, which called for budget impact analyses for formulary submissions.

Mauskopf says around 2001, she was asked to start teaching budget impact analysis courses before the yearly ISPOR meetings. "It did seem like there was a need for that, so I sort of stepped into that breach, working at first with Daniel Mullins and later also with Stephanie Earnshaw."

What started out as one course became two courses with consistently

AWARDS

high enrollments, and since then, "My colleagues and I have taught multiple generations of health outcomes researchers the fundamentals of budget impact analysis. Our costing approach is population-based and includes estimation of the clinical outcomes at a population level within the analysis time period."

Despite the years of teaching, Mauskopf does not claim to be a great teacher. "Teaching is not my greatest skill, actually," she says, which is why she recruited C. Daniel Mullins, PhD, chair of the Pharmaceutical Health Services Research Department at the University of Maryland School of Pharmacy, to teach the courses with her. "I felt that I needed a real teacher, and he is better at it than I am."

In addition to teaching, Mauskopf has helped write the definitive textbook on budget-impact analysis, *Budget-Impact Analysis of Healthcare Interventions: A Practical Guide*. The book, published in 2017, is the first of its kind for budget-impact analysis. Mauskopf is coauthor, along with RTI's Stephanie R. Earnshaw, Anita Brogan, Thor-Henrik Brotkorb, and Sorrel Wolowacz.

For ISPOR, she has been a member of the 2013 CHEERS task force, cochair of 3 task forces: (1) Budget Impact Analysis 1 in 2007, the results of which were used as a reference for the Canadian budget-impact guidelines; (2) Budget Impact Analysis 2 in 2014, used as a reference for the French guidelines; and (3) Economic Evaluation of Vaccination Programs in 2018, the results of which have just been published in *Value in Health*. The latter "is innovative in that it provides guidelines for three different methods of economic evaluations (ie, cost-effectiveness analysis, constrained optimization, and fiscal health modeling) and proposes that the different methods can be useful in different decision contexts, extending our ideas about economic evaluation beyond cost-effectiveness analysis," Mauskopf says.

Besides the premeeting courses, she has taught issues panels and workshops on a variety of topics, including competitive bidding, league tables, and multi-criteria decision analysis. And since the founding of ISPOR, she has presented papers and podiums at almost every meeting since 1998, including economic evaluations in multiple therapeutic areas (infectious disease, cardiovascular disease, neurological disease) and methodological literature reviews (adherence to HTA guidance and methods for cost-of-illness studies).

When it comes to taking advantage of the opportunities ISPOR provides, her best advice to new professionals and long-time members is simply, "Don't wait to be asked. Just get involved."

From 2014 to 2016, Mauskopf has served on the Board of Directors and the Publications Management Advisory Board, where she helped move ISPOR forward as it transitioned from Marilyn Dix Smith's leadership to Nancy Berg's leadership. And from 2013 to the present, she has been on the ISPOR Health Sciences Policy Council and a member of the Avedis Donabedian Award selection committee.

A Mentor to Others

According to Daniel Mullins, the 2017 winner of the Marilyn Dix Smith Award, Dr Mauskopf "is always interested in helping others."

"Jo has a wonderful balance between an outstanding researcher and a committed mentor," Mullins says. "She exemplifies the spirit of leadership, so it is a great testimony to her to receive the prestigious Marilyn Dix Smith Award. On a personal note, I also appreciate the opportunity to learn from her, having served as an associate editor under her leadership of *Value in Health* and as a co-instructor in various ISPOR programs."

Diana Brixner, PhD, RPh, professor in the Department of Pharmacotherapy and executive director of the Outcomes Research Center at the University of Utah College of Pharmacy, wrote the nomination letter for Dr Mauskopf and submitted it to the Marilyn Dix Smith Award committee.

"Dr Jo has been a foundation for ISPOR over the many years she has served the organization," Brixner says. "Her contributions to the high-quality task forces, deliberations during various ISPOR venues at our international meetings, and her contributions to communication worldwide through *Value in Health* have promoted the science of health economics and outcomes research and provided tremendous mentoring opportunities to the many that will follow her lead."

When it comes to mentoring and teaching, Maukopf says, "I try to encourage people to think." When working with her younger colleagues in doing overall guideline reviews, she has noticed they tend to present spreadsheets with a lot of information, but little in the way of conclusions that synthesize their findings. "When I am working with younger people at RTI, I encourage them to pull out of the weeds, the learning from it, and not just present huge tables that don't help very much," she says.

What the Marilyn Dix Smith Award and ISPOR Mean to Her

This is not the first time Maukopf has been honored by the organization. She received the ISPOR Award for Excellence in Application of Pharmacoeconomics and Outcomes Research in 2006, and the ISPOR Avedis Donabedian Lifetime Achievement Award in 2013.

But Mauskopf was also close to Marilyn Dix Smith, who passed away in 2018, so receiving this award has additional meaning for her. "I'm just honored to get it, because I think she was a wonderful person," Mauskopf says. "She was someone who not only had the broad vision of setting up something, but she also took care of the nitty gritty. She

AWARDS

was just an inspirational person. Her openness to new ideas made ISPOR an amazingly flourishing organization and her attention to detail made it financially very solvent as well."

ISPOR has been the only professional society she has ever joined. "I feel very grateful to ISPOR for giving me the opportunities that it's given me—to be a journal editor, to teach courses, and to interact with all of the other amazing people—so I think ISPOR has made a huge difference for me in allowing me to do what I've done."

For those new in the health economics field, she says, "the way to advance your career is take something that's of interest—that you have some experience in—of importance and build around it. Sell yourself as having this experience and this expertise. Once you have some projects doing that, you have more experience and you will eventually become an expert in it. It's a way of saying, 'What other sort of ideas or prior experience do I have that I can see is going to be of value?"

ISPOR provides many opportunities for young health economists to build upon their experience, with multiple task forces that are more open to junior people joining and contributing. "At ISPOR, when I've been in groups, we've talked quite a bit about how you don't want the same people all the time, even though you know they're experts," Mauskopf says.

It was ISPOR's openness to new people and ideas that got her involved in *Value in Health*, she says. "They were having an organizational meeting, it was brand new and it was open, so I went."

When it comes to taking advantage of the opportunities ISPOR provides, her best advice to new professionals and long-time members is simply, "Don't wait to be asked. Just get involved."

ISPOR Scientific Achievement Awards: Call for Nominations

The ISPOR Awards Program is designed to foster and recognize excellence and outstanding technical achievement in pharmacoeconomics and outcomes research. These awards will be presented at ISPOR 2020, May 16-20, 2020, Orlando, FL, USA.

The ISPOR Avedis Donabedian Outcomes Research Lifetime Achievement Award
Established in honor of the late Avedis Donabedian MD, MPH to acknowledge those individuals who have made a major contribution to the improvement of health outcomes. *For complete details, see www.ispor.org/avedisaward.*

ISPOR Marilyn Dix Smith Leadership Award
This award is international in scope and stature, recognizing one individual each year who has provided extraordinary leadership to the Society. *For complete details, see www.ispor.org/mdsaward.*

ISPOR Bernie O'Brien New Investigator Award
Established in 2004 to honor the long-standing commitment of Bernie J. O'Brien, PhD to training and mentoring new scientists in the fields of outcomes research and pharmacoeconomics. *For complete details, see www.ispor.org/obrienaward.*

ISPOR Health Economics and Outcomes Research Excellence Award-Methodology
ISPOR Health Economics and Outcomes Research Excellence Award-Application
Established in 1997 to recognize outstanding research in the field of health economics and outcomes research methodology and outstanding practical application of health economics and outcomes research in healthcare decision making. *For complete details, go to www.ispor.org/awards.*

All Nominations Due by February 7, 2020

Nominations can be submitted at www.ispor.org/awards.

AWARDS

What Does it Take to Be an Outstanding ISPOR Regional Chapter?

An Interview With the ISPOR 2019 Outstanding Chapter Award Winners: Colombia, Russia St. Petersburg, and West China Chapters

The ISPOR Outstanding Chapter Award program recognizes ISPOR regional chapters' outstanding contribution and leadership in advancing ISPOR's mission in global regions: Asia, Latin America, and Europe, Middle East, and Africa. The ISPOR Colombia and St. Petersburg chapters have been recognized for the second time for their exemplary achievements in advancing health economics and outcomes research (HEOR) in their region. The award is based on a thorough review of chapters' compliance with ISPOR governance, input to ISPOR publications, and contribution to ISPOR activities throughout the year as described in their annual reports.

Editor's Note:
Value & Outcomes Spotlight talked to the presidents of ISPOR regional chapters that were recognized with this year's Outstanding Chapter Award and asked them to reflect on their overall performance, the impact of digital health on healthcare delivery, and the top 10 HEOR trends in their regions.

Congratulations on being recognized with the 2019 ISPOR Outstanding Chapter Award. This award demonstrates continuous active engagement and contribution of your chapter to advancing HEOR and informing relevant health decision-making processes. What do you believe are the essential factors to your chapter's outstanding performance, and what advice would you offer to other regional chapters in your category who are seeking to deliver value and keep their members engaged?

Camilo Castañeda-Cardona, MD, president, ISPOR Colombia Chapter, NeuroEconomix and IdeaXplore, Bogotá, Colombia
After 10 years of hard work, we have reached an important leadership position in the region and currently have more than 100 members. This makes us very proud. The essential factors of our performance rely on 2 key aspects: (1) **Efficient leadership**. Our chapter has had presidents and boards of directors committed to giving our members the greatest possible value, which is translated into events, training, and discussion opportunities with all actors in the health system. The board of directors has understood the evolution and challenges of our health system and how, through ISPOR, we can contribute and create. (2) **Activities and educational value**. The ISPOR Colombia Chapter is committed to the dissemination of knowledge in pharmacoeconomics and outcomes research. That is why we have been developing face-to-face and online courses, workshops, webinars, congresses, and other valuable meetings for our affiliates. This is key to maintain our audience and keep attracting more members to the chapter.

Alexey Kolbin, MD, PhD, president, ISPOR Russia St. Petersburg Chapter, Department of Clinical Pharmacology and Evidence-Based Medicine, First St. Petersburg State Medical University n.a. academician I.P. Pavlov, St. Petersburg, Russia.
It is a big honor for us that our activities are recognized by ISPOR. Our chapter is recognized with the award for the second time and this is a clear message for us that we are on the right path in developing not only the chapter but following the ISPOR philosophy in healthcare decision making, which is based on the balance of clinical effectiveness and economic expedience. In my mind, the key factor of our success is the cooperation of several academic bodies: First Saint-Petersburg Sate Medical University n.a. acad. I.P. Pavlov, North-West State Medical University, Saint-Petersburg State University and RUDN University. I think our key advantage is the multimodality team including not only clinical pharmacologists but also statisticians, mathematics, and healthcare managers. I would advise all regional chapters to think big and seek cooperation with colleagues from different regions. Furthermore, just like in boxing, we are planning to move in to the next weight, by that I mean the medium-size chapter award category, and become champions in it.

Xin Sun, PhD, president, ISPOR West China Chapter, Chinese Evidence-Based Medicine Center and Cochrane China Center, West China Hospital, Sichuan University, Chengdu, China.
We are very honored and excited to receive this prestigious award from ISPOR. The success of our chapter is firstly attributable to a strong leadership team. In our governance structure, each director is responsible for 1 of the 4 research areas, including real-world data and evidence, pharmacoeconomics, drug policy on special populations, and rational drug use. The directors are delegated to develop special interest groups around their areas. Secondly, we are striving to develop academic leadership. In developing the real-world evidence initiative, we have taken the lead in establishing China Real-World Data and Studies Alliance (ChinaREAL) through largely engaging chapter members, developing groundbreaking technical guidance documents for real-world evidence studies, convening national data partners, and organizing serial national congresses on real-world evidence—all of which help shape our leadership in China's real-world evidence developments. Thirdly, we have a strong mission by translating evidence into clinical and health policies. In our continuing efforts, we have developed strong collaborations with governmental authorities, such as the National Medical Products Administration, the National Health Commission, and the National Healthcare Security Administration.

AWARDS

We know that digital health is high on the agenda of improving healthcare delivery and improving patient outcomes. What impact do digital health technologies have in your country in improving patient outcomes? From a global perspective, what are the major challenges in digital transformation of healthcare?

CC: In Colombia, decision makers (especially insurers and service providers) have been progressively implementing digital tools to optimize processes, typify their patient populations, and measure their performance in the provision of services. This, in general, optimizes the use of resources and impact on clinical outcomes. However, the challenges are huge. The technological systems in Colombia are broken down. There is not a single platform of medical records, and the information that each actor collects is not analyzed in a deep and comprehensive way to make better decisions. We have certainly made progress, but we still have a long way to go. The need to produce real-world evidence with Colombian population is urgent.

AK: You are right, the role of digital healthcare is one of the main challenges for all healthcare systems around the world. In Russia, this topic is discussed by several experts groups. One of the most well-known players in this field is the Association of Developers and User of Artificial Intellect in Medicine's medical knowledge national database. This project is joining several companies with their digital products and independent experts. The main goal of the project is the creation of the system of medical competences transfer—that is, an integrated system of the support of decision making in medicine and healthcare not only at the patient-bed level but at higher levels, too. Our chapter is involved in this work through the Association of Clinical Pharmacologists of Russia.

XS: Digital health has become a fascinating concept in the Chinese healthcare systems. Although its development is at the early stage, the impact of digital health technologies on healthcare has become extensive and substantial. In the use of routinely collected healthcare data, scientists and clinicians are interested in developing prediction models to assist the diagnosis and the management of cancer. Attempts also have been made to combine such tools or medical literature with an electronic medical records platform to develop integrated clinical support systems. Meanwhile, mobile devices are in wide use for monitoring blood pressure and glucose for the management of chronic diseases. In the population level, the real-world evidence initiative (through the use of healthcare big data) is redefining the evidence about healthcare interventions, including treatment patterns and compliance, safety, and comparative-effectiveness and cost-effectiveness, thus advancing healthcare policy decisions. Despite these merits, the quality and completeness of healthcare data continues to be the obstacle. The existing disparities, particularly socioeconomic imbalances across the regions and countries, will also challenge the successful digital transformation of healthcare.

When ISPOR released its "2019 Top 10 HEOR Trends," the issue of "spending and pricing" ranked the number 1 this year. The results were based on a survey of ISPOR members. How do the global HEOR trends translate to the situation in your region? Is there much overlap?

CC: I believe that spending and pricing are key issues in our region and the country. Latin America has great challenges in financing and sustainability, and this is directly related to this issue. I believe that other key issues for us in the region are "value frameworks," "price transparency," and "real-world evidence." I consider that issues such as "equity" and "financing in high-cost therapies" such as cancer and rare diseases would be in a local ranking at the top of the list since they are currently considered as key concerns. This is not because the other items are not relevant, but because there are key aspects of our health systems such as sustainability, value-based pricing, and transparency that are not yet functioning efficiently and require more work and progress.

AK: In our region, the most important are real-world evidence and big data. In particular, I have to tell you that the Association of Clinical Pharmacologists of Russia is planning to build national real-world evidence concept (like the US Food and Drug Administration's Real-World Evidence Program) and we have already started this work. For us, it is very important to know the experience of other ISPOR members and chapters in this field. We are open to collaboration and cooperation.

XS: Healthcare reform in China has a strong interest in reducing healthcare expenditures. As such, the governmental authorities have taken measures to deal with excessive spending on medical products in order to improve accessibility and affordability. These efforts may include the removal of drug price top-up by hospitals, lowering the proportion of drug costs among medical expenditures, and extending health insurance coverage to special health problems, such as cancer and rare diseases. To achieve these goals, efforts have been made to negotiate drug prices in recent years. Along with the global trend, rigorous approaches have been widely used for policy decisions in China. For instance, health technology assessment framework and process are becoming a desirable approach in the selection of insured drugs. At the end of 2018, the National Health Commission and the National Healthcare Security Administration achieved a consensus that health technology assessment should be enforced in medical insurance access.

About ISPOR Regional Chapters

ISPOR is committed to supporting HEOR advancement and healthcare decision making for health globally. This mission is reflected in ISPOR's global HEOR community of more than 20,000 individual and chapter members from 120+ countries around the world. ISPOR regional chapters facilitate the global flow of information related to healthcare decision making. There are currently 86 ISPOR regional chapters in global regions. For more information, go to www.ispor.org/member-groups/ global-groups.

The Balance Between Affordability, Value and Access

BY MICHELE CLEARY

Ever-growing healthcare spending is at risk of crowding out much-needed investments in infrastructure, education, and public health sectors. As discussed in a recent issue of *Value & Outcomes Spotlight*, aging populations will continue to challenge healthcare budgets. A 2017 study in the *Journal of the American Medical Association* noted that aging accounted for an 11.6% increase in US healthcare spending between 1996 and 2013.[1] In addition to growing demand due to aging populations and the rising prevalence of chronic conditions,[2] health systems around the globe are confronted with the release of more sophisticated and higher-priced medical technologies and drugs. In 2017, biologic drugs represented 2% of all US prescriptions, but 37% of net drug spending.[3] These spending trends show no signs of slowing. The Centers for Medicare & Medicaid Services's National Health Expenditure Projections 2018-2027 Forecast Summary predicts that the health share of gross domestic product (GDP) in the United States is expected to increase from 17.8% in 2019 to 19.4% by 2027.[4]

Decision makers are struggling under budget limits, trying to ensure access to effective treatments while keeping such care affordable. The balancing act begins when evaluating the value of a new medical technology—whose perspective taken, what threshold level should define value, when should the medical budget expand to accommodate new technologies? Trade-offs between perceived value and the ability to afford a new therapy given budget constraints often drive access to new innovations. The interconnection of value and affordability at a system level and how this impacts access to medical technology and pharmaceuticals may be the most challenging problem faced today by this audience.

The 2018 ISPOR Summit examined value frameworks from a variety of perspectives. HEOR researchers often focus on defining the "value" of medical technologies from various viewpoints. However, we are seeing that the ability to pay for such new innovations depends a great deal on how the payer defines its budget and the trade-offs payers make in order to ensure or deny access to treatments of value deemed to be insufficient to displace an established therapy. These conflicts cannot be ignored in the value judgment. More research is focusing on how to determine "willingness to pay" from different viewpoints and how that can be turned into thresholds used to objectively evaluate and compare value often measured by cost-effectiveness methods.

This article talks with some thought leaders in this field, to hear their concerns and proposed ideas about how health systems may better address these conflicts. For this article, A. Mark Fendrick, MD; Chuck Phelps, PhD; Joshua Cohen, PhD; and Stephen Schondelmeyer, PharmD, PhD shared their thoughts on this debate.

Concerns regarding the current value methods

Faced with limited healthcare budgets, stakeholders are more comfortable with the view of value—if price for healthcare service or product is at or below a defined threshold, then we are getting value for money spent in our healthcare system. Yet many have voiced concerns regarding how value is determined, especially those surrounding quality-adjusted life year or QALY.

Stephen W. Schondelmeyer, professor of Pharmaceutical Economics in the College of Pharmacy at the University of Minnesota, shared his concerns with the QALY approach, namely where thresholds are set. He noted that the QALY threshold used by ICER now reaches $150,000—a value significantly greater than the US median income. He argued, "If we assume that a value of a QALY is twice the median income in society, that sets up a structural deficit for the US economy. We're going to continue to spend more and more on healthcare than we have in total resources, and healthcare will grow so much that it chokes out other things in our economy." While some survey research has been conducted to help identify society's willingness-to-pay for services, he noted that these survey respondents tended to be better educated, wealthier people, who may view a QALY as worth more than a generalizable population.

Some assumptions used in cost-effectiveness analyses (CEA) also concerned Schondelmeyer. He finds that CEA models assuming that all patients received optimal care artificially inflate the cost savings from a new treatment given that optimal care is often more intensive than the level of care received in a real-world practice environment. He argued that these differences become especially pronounced when treatment benefits are modeled over a long time-horizon.

Schondelmeyer finished by voicing his concerns over cost models based on initial prices. Given that the rate of inflation in drug prices often far outpaces the rates of wage increase, the cost-effectiveness of a new treatment versus the standard of care is artificially high in these models and is further compounded over a five- or ten-year time-horizon.

While Schondelmeyer believes in value assessment models, in determinant values, he argues that they must be based on assumptions that are realistic and they must acknowledge that there is a limit to the resources we could spend on healthcare, stating, "I don't think we have a system in America that establishes prices that are truly based on the net value that someone would actually pay and based on the quantity of resources available to pay for it."

The problem with increasing the threshold

Charles E. Phelps, former provost of the University of Rochester, added his concerns regarding QALY thresholds, but thresholds in relation to budgets (defined as the maximum level at which you're willing to pay for healthcare).[5] Phelps argued that cost-per-QALY thresholds cannot be set independent of the budget. "My view is the budget is the relevant story," said Phelps. "You have to figure out what you can buy within that. And that really is the operational cost per QALY that you're willing to pay for."

Specifically, Phelps found the practice of increasing the thresholds for specific services misguided. As an example, he cited the British Health Service practice of increasing the cutoff threshold for end-of-life care, rare diseases, and pediatric diseases. Instead of arbitrarily changing these thresholds, he argued that once the thresholds are set, health systems must be able to say "no" to those products or services exceeding that threshold.

Phelps spoke of institutionalized US Medicare policies that preclude the Centers for Medicare and Medicaid aServices (CMS) from adequately rejecting treatments that exceed defined thresholds. The Social Security Act states that Medicare shall pay for all treatments that are "necessary and reasonable." That is the only language that guides CMS in terms of what they shall allocate. Similar policies bind the US Food and Drug Administration, as cost cannot be considered as a condition for approval of drugs, devices, or other biological products—only safety and efficacy. But he stated that CMS could be empowered with the ability to consider value, to use cost-effectiveness criteria in deciding what to cover, with a simple one-line modification to the Social Security Act. However, no such amendments are currently considered. >

Phelps emphasized that these examples reveal an important concern surrounding thresholds and value. "That's telling you something's missing from the standard cost-effectiveness formulation. Instead of saying 'how do we measure that value,' they're saying, 'we're going to relax the threshold.' You either say this is more valuable, and I know why and here's by how much, or you say, I know that's more valuable, but I don't know how, so I'm going to relax my threshold. To me, that's a signal that the cost-effectiveness model is incomplete."

For this, he has been advocating multiple criteria decision analysis (MCDA).[6-8] MCDA provides an alternative to CEA. It formally incorporates additional dimensions of value beyond those normally used in CEA to help make the final decisions about new technologies. Phelps noted that MCDA has not yet gained much traction in either the United States or in Europe. However, he encouraged this audience to embrace these new approaches. "It's coming," Phelps said. "If you want to make it more realistic, work to help make it better. Don't jam your foot on the brakes, because it's coming down the train tracks."

Differing views of value

Joshua P. Cohen, an independent healthcare consultant, echoed some of the previously mentioned concerns surrounding the QALY thresholds, noting that the threshold is arbitrary. "If not empirically determined, it's not necessarily value-based," said Cohen. But beyond the thresholds, he emphasized that the consensus across a truly representative round table of stakeholders regarding the "terminology of value" is needed. "Not just patients, not just doctors. But payers, policymakers, drug makers." The 2018 ISPOR Summit reinforced the importance of input from a broad mix of stakeholders when assessing value.

Cohen discussed the issue of protected drug classes as a demonstration of what happens when broad representative consensus is not considered. Medicare currently requires health plan sponsors include all drugs in 6 protected drug classes in their formularies. These protected drug classes include antidepressants, antipsychotics, anticonvulsants, immunosuppressants for treating transplant rejection, antiretrovirals, and antineoplastics.

But he points out that by being required to cover all drugs in those protected drug classes, plans are limited from negotiating over price. "That, of course, is not value-based." He noted that a drug company could simply set the price, and the insurer has no choice but to cover that drug, regardless of whether it is better than the standard of care. "And that to me is really skirting the whole issue of value and value-based pricing."

Cohen stated, "(Payers) should at least have been at the table when it comes to these protected drug classes to make sure that the monopoly price…because that's what it becomes when the drug industry can set the price really as it wishes, without any fear of competition. They should have been at the table to at least discuss ways in which they could still have some leverage."

He reinforced the value of gathering a broad mix of stakeholders in these decisions. "If we can do that, then we're really well on our way to value-based pricing, but I don't think we're there yet."

Nonetheless, Cohen still is committed to QALY measure, "The QALY measure itself I think is the best we have, there certainly are criticisms, but it's the best we have at this stage."

Value-based insurance design

A. Mark Fendrick, professor in the Department of Internal Medicine and Department of Health Management and Policy at the University of Michigan, summarized his long fight to bring more intelligence into how healthcare stakeholders spend their healthcare dollars. "There is very good news when you're talking about healthcare," Fendrick began. "Everyone agrees that there's enough money in the system. And just about everyone agrees that we are spending some of it—maybe a lot of it—in the wrong places."

Fendrick is the director of the Center for Value-Based Insurance Design (V-BID), which promotes the development, implementation, and evaluation of health benefit designs that balance cost and quality. V-BID is built on the principle of lowering financial barriers to essential, high-value clinical services. He cites V-BID benefit design initiatives to ensure consumers "not have the low-value things be low-price things, but instead have the low-cost things be high-value things."

How can we afford high-value, high-price treatments?

Fendrick notes that expanding coverage of cost-effective care (eg, disease management services for hypertension, HIV, or depression) is not sufficient. As policymakers now recognize, expanding coverage of cost-effective care does not reduce total costs. And purchasers were demanding a V-BID plan that was cost-neutral.

To expand coverage for most any new treatments, plans could either raise premiums on healthy people, increase cost-sharing included deductibles (which Fendrick calls a tax on the sick), or decrease access to low-value care. This is the approach Fendrick believes should be the focus of the current value debate—removing no-value or low-value care in the system. Says Fendrick, "The good news is there's a lot of no-value care in the system. The bad news is there's a lot of no-value care in the system."

The reallocation message

While researchers have long focused on the high-value quadrants, Fendrick argues that more attention should be focused on those services that are in the low-value quadrants, stating, "People love to talk about the dominant situations (eg, save lives, save dollars) that rarely/never happen. But there's a whole bunch of things in a don't help/cost money quadrant." These low-value quadrants can be massive, as shown in a 2010 study by the Institute of Medicine showing 30% of healthcare spending in the United States was wasted on low-value and potentially harmful health services.[9]

By cutting investment of healthcare dollars in these low-value quadrants, Fendrick argued that new (high-price) treatments could be covered. This reallocation method is the basis for his V-BID benefit design.

Fendrick pointed to the V-BID Ex (ex for exchanges) product, which lowers cost-sharing on 20 high-value services by raising

cost-sharing on low-value services, achieving dollar-for-dollar coverage. He highlighted, "Premiums did not go up, deductibles did not go up. Access to high-value services went up and paid for entirely by decreasing access to low-value care."

The V-BID approach could address a core concern voiced by Cohen—cost-sharing that hinders treatment adherence. As Cohen stated, "if you have something that's really valuable, say it's a diabetes medication and needs to be taken on a daily basis in order for it to have that value, then you need to reduce the copayments, preferably to zero." V-BID would help treatment adherence of these high-value therapies by minimizing cost-sharing on these high-value interventions.

V-BID's reallocation approach is rapidly gaining wide support. Fendrick announced that V-BID design had been received by numerous states. "We are hopeful by the 2021 plan year we'll actually see V-BID Ex-type prototype plans available to individuals on the individual marketplace, and hopefully that will spill over largely to more public and private payers." V-BID will be implemented in numerous Medicare demonstrations, in TriCare, and is now taking hold in the commercial marketplace. "There's more than enough money in the system. Who's against more of the good stuff and less of the bad stuff? I think that my goal is having providers and consumers aligned around value."

He stated that he hopes public and private purchasers will "follow the lead of hundreds of public and private payers across the country and take a hard look at their benefit designs and align cost-sharing with clinical value, not price. We have every reason to believe that V-BID implementation will continue to be slow and steady."

ISPOR and affordibility, value, and access

Both Phelps and Fendrick see ISPOR members playing an important role in the value debate.

Said Fendrick, "The ISPOR members need to know that as we continue to get payments and benefit design to be driven by clinical value, the work of ISPOR members will become increasingly relevant and implemented in the real world." He continued by saying, "That is what they do. They determine relative value of services. And they should be more actively involved in this clinically driven payment reform and benefits design. They should continue to refine the methodology." ISPOR members realize that funds are not unlimited, he stated, and "they can apply their expert methods to the identification and reduction of care that we shouldn't be buying so that we might create headroom to be able to purchase more of the things that we know improve the health of individuals and populations."

He closed by saying, "People really like the reallocation message. Everyone agrees with more of the good stuff and less of the bad stuff. Who should be the arbiter? The arbiter of good stuff and bad stuff? Why not ISPOR?"

Phelps sees ISPOR researchers as key in the development of value assessment methods, stating. "I would welcome the participation of people in industry to improve these methods. They're not perfect. MCDA methods are far from perfect. They're very clunky and hard to use. And cost-effectiveness is incomplete." He noted that some in this space have warned against the premature use of some value assessment models. But Phelps encouraged the ISPOR audience to venture ahead with these new methodologies, using his previously published Wright Brothers analogy.

"The Wright Brothers' first flight went a distance less than the wingspan of a Boeing 737. They made 6 flights that day. By the time they'd finished their sixth flight, that distance increased by a factor of 7 or 8 through experimenting and tinkering. You can't make these things better without using them."

"If they had said we have to perfect this tool before we use it, we would still be taking the train."

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About the Author

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By the Numbers: Balancing Affordability, Value, and Access

Section Editor: The ISPOR Student Network

Milestones for value-based care in the United States

2008 Medicare Improvements for Patients and Providers Act passed[1]

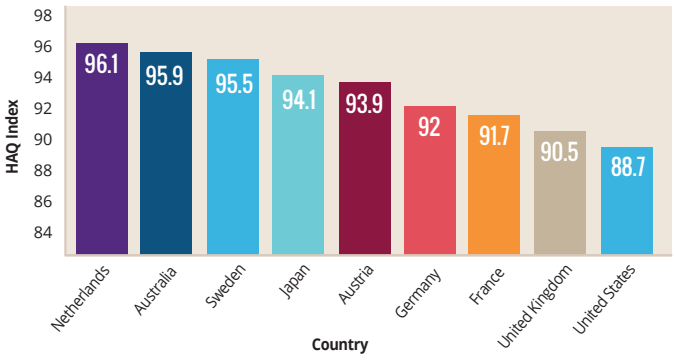
2010 The Affordable Care Act is passed that would later institute the Hospital Value-Based Purchasing Program (HVBP) and Hospital Readmission Reduction Program (HRRP)[2]

2012 The HVBP and HRRP released by the Centers for Medicare and Medicaid Services (CMS) that focus on reimbursing hospitals based on quality of care[3,4]

2015 The Medicare Access and CHIP Reauthorization Act is passed, changing Medicare reimbursement for clinicians from volume-based to value-based care[5]

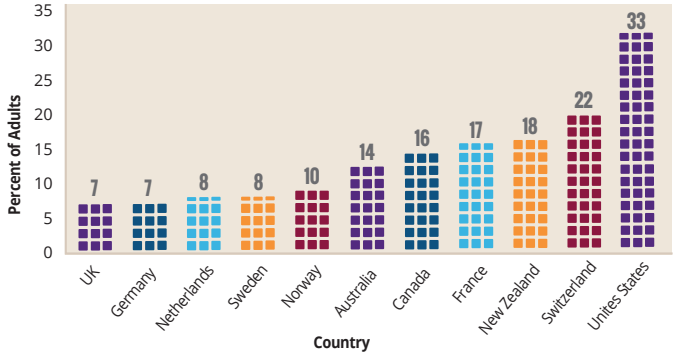
2019 Merit-based Incentive Payment Systems released by CMS, which will ensure that eligible physicians earn a value-based payment adjustment for their Medicare payments[6]

Healthcare Access and Quality (HAQ) index rating for countries, 2016 [7,8]



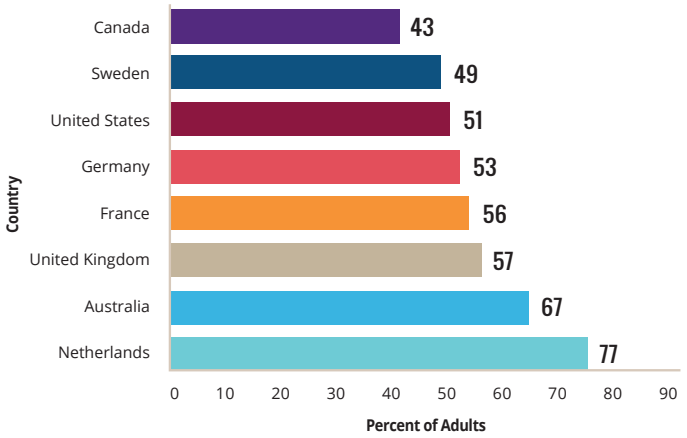
HAQ Index: Encompasses 32 causes of death considered to be avoidable provided that quality healthcare is available. These causes include a range of health service areas: (eg, vaccine-preventable diseases; infectious diseases and maternal and child health; non-communicable diseases, including cancers, cardiovascular diseases, and diabetes; and gastrointestinal conditions from which surgery can easily avert death, such as appendicitis.)

Adults with cost-related access barriers by country, 2016 [9]



Examples of cost-related access barriers include instances where patients had a medical problem but did not visit doctor; skipped a medical test, treatment or follow-up recommended by a doctor; and/or did not fill prescriptions or skipped doses.

Percent of adults (≥ 18 years old) who were able to make a same-day or next-day appointment when they needed care by country, 2016 [9]



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Lies, Damned Lies, and Cost-Effectiveness: Open-Source Models Are Essential if Cost-Effectiveness Analyses Are to Be Widely Accepted

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Cost-effectiveness models synthesize a wide range of evidence and require assumptions that are not directly testable. Open-source models encourage greater transparency in pharmacoeconomic modeling and allow faster access to critical knowledge.

Health economic models go beyond what we can directly measure within randomized controlled trials and help determine the full value of a technology by synthesizing a wide range of evidence to facilitate extrapolation over time and from intermediate to final decision endpoints.[1] They help us to make trade-offs between risks, benefits, and costs. These models are often statistically sophisticated and make assumptions that are not directly testable. This can lead to decision makers "discounting" their results, particularly if the developer is seen as partial, the modeling assumptions and "guts" are not transparent, or if it is unclear how the results were derived.[2] Indeed, the *New England Journal of Medicine* in 1994 derived their policy on publishing cost-effectiveness models by stating that "some cost-effectiveness analyses are funded by companies that hope these analyses will put their products in a favorable light. Companies might even use this favorable analysis to justify the price of their drug."[3] By the same token, patient groups may be skeptical of health technology assessment (HTA) body rulings. How, then, to allay these concerns and develop models that are believable and allow for credible decision making?

Making these models "open-source," in the sense that all code is openly viewable and available, has the potential to address some of the concerns of decision makers and to improve the quality of economic evaluations by both allowing investigators to access a range of candidate models and facilitating the internal validation of these models.[4,5] The analogy here is that of "shining a light" on the model to illuminate its inner workings. Indeed, the United Kingdom Court of Appeals ruled that the UK's National Institute for Health and Care Excellence (NICE) should release a fully executable copy of a model used in an appraisal of a treatment for Alzheimer's disease in order to comply with the principle of procedural fairness.[6] A survey of a small segment of the UK public ranked the characteristics of procedural justice—accuracy, consistency, impartiality, reversibility, and transparency—in terms of their importance to public healthcare resource allocation.[7] If public decisions are to be seen as socially just, the people affected by those decisions need to be able to question them, to ascertain that these models are fair and that consistent decisions are being made. Mistakes can easily be made and only by making these models "checkable" can one illuminate these potential errors. The formation of the Open Source Initiative (OSI), the main accrediting body for open-source software, was largely driven by concerns with finding and correcting bugs. OSI accreditation requires meeting 10 criteria, among which are (1) free distribution, (2) provision of source code, and (3) allowance of modification and derivative forms. Although OSI does allow for protecting the integrity of software by keeping the derivative forms separate from the original model, this third criterion may be of concern in our field.

Some organizations require parties other than the original developer to vet models, they hope to use. For example, the US Department of Defense has many models, and vendors are required to have their models verified, validated, and accredited.[9] Among the recommendations of the ISPOR-SMDM task force on good modeling practice,[10] several tenets held that:

- trust and confidence are critical to the success of models
- technical documentation must be made available in sufficient detail to be evaluated and reproduced
- source code of the model must be made available either openly or by anyone under a nondisclosure agreement

And yet, distrust of models persists. Six years later, a member of one of the evidence review groups for NICE stated that he felt all of the submitted models were highly biased.[11] >

Nevertheless, models in our field are rarely openly available. This may reflect concerns (real or perceived) with the potential impact on intellectual property rights, trust issues, and the effort involved in developing and maintaining them.[8]

The remainder of this article details some of the issues and barriers to broad implementation of open-source models in healthcare.

Health economic models go beyond what we can directly measure within randomized controlled trials and help determine the full value of a technology.

Issues

Why are other models (eg, NASA path to Mars, trajectories for hurricanes, quantitative Wall Street predictions) not pressured to be open-source? The reason is that life provides validation of these models: their inaccuracies are soon evident. Unlike these models, those used in health economics are not easily subject to refutation as the outcomes are typically not directly observable and we do not see the counterfactual (eg, what would have happened had the patient received an alternative treatment?). Thus, they need to be explicitly validated. This can be quite difficult to achieve convincingly because data tend to be sparse and the effort involved is substantial.[12] Without diminishing the importance of validation, we propose that all models that are being used to support healthcare decisions be made available for anyone to see, including the source code, a detailed technical report, verification report, and results of any validation exercises. Whether redistribution, modification, or creation of derivative works should be allowed without restriction is at issue. This last point brings up a number of barriers to adopting open-source models.

Barriers

Concerns with opening up the "guts" of health economic models to scrutiny by people other than the creators and/or sponsors have been expressed. The issues fall into the following buckets:

- intellectual property rights/payment
- whom to trust
- model access (terms, means, versioning)
- model storage/maintenance/updating

Not included here are issues of data confidentiality and legal and regulatory concerns, which are beyond the scope of this review. Each of these above points is explored separately below.

Intellectual property rights

To understand intellectual property barriers, it is necessary to explore the distinction between proprietary and open access software. Proprietary software is developed and owned by an individual or entity. The "source code" is kept secret and is protected by copyright. If someone wants to use the software, they have to enter into a license agreement with terms that restrict any modification of the software or distribution to others. Think of any Microsoft license or any other license you have "clicked to accept." In contrast, open-source software makes the source code openly available to others who can use it without restriction, troubleshoot, build on it for their own analyses, etc (Figure 1). There are several forms of open-source licenses (eg, the MIT license), but in general, they grant users permission to view and use the software for any purpose they wish.

Some open-source licenses are what people call "copyleft" licenses, which stipulate that anyone who releases a modified open-source program must also release the source code for that program alongside. Some open-source licenses stipulate that anyone who alters and shares a program with others must also share that revised code without charging a licensing fee. These are the aspects of open-source that may concern those who do not want to expend effort on developing a model yet allow others to derive works from which they can profit.

Figure 1. Crowdsourcing

Trust

Open-source software encourages others to access, view, and modify it. With this open exchange, someone might spot and correct errors or omissions that a model's developers might have missed, and this may be done more expediently than otherwise. How does one determine whom to trust with the code: whether the potential user is sufficiently knowledgeable about the disease state, the type of model, and the rationale behind model development? Will they use it or modify it "correctly?" Who determines what is the "correct" way to use or modify it?

Figure 2. Model access

Model access (terms, means, versioning) (Figure 2)

Model developers might share published models that may, in turn, require permission from any number of stakeholders—data holders, publishers, sponsors, grantors, and codevelopers. These stakeholders may have different reasons and incentives for not allowing model access "freely," that is, without encumbrances. Some concerns about model access are as follows:

1. Terms of access: On what terms will users gain access? Free, by fee, time limitations, restrictions on use, recovery of expenses? Can an institution access it, or will only individual licenses be acceptable? Can a license fee be charged

so that the developer(s) feel fairly compensated, but is not so onerous that use by others becomes cost-prohibitive? Even more crucial, what is the incentive for the developer to maintain the model they have made available and to keep it current? Who will adjudicate copyright and other use issues? Will it be by panel or by individuals? If by panel, who will comprise the panel? Will this process be partially or fully automated to make it less onerous to developers and users?

2. Means of Access: Perhaps most important are the logistics for making open-source models available. Where will the model be stored—on the developer's or other secure server and accessed remotely only, or downloadable to the user's computer?

3. Version control: Who will maintain the model and control versions? If an apparent error is found in the model, who verifies it, corrects it, and with what incentive? If there are multiple modifications, will these be integrated into one version and by whom? Or, who will determine which modifications to make?

Although the topic of open-source models in health economics is garnering attention, a cultural shift in model development is necessary to ensure these see the light of day. Questions remain as to who will lead this shift from proprietary to open-source models and how this can be encouraged in a culture where secrecy, competition, and one-upsmanship have been the norm. ISPOR is making strides in this regard, including the initiation of the Open Source Model Special Interest Group that will attempt to tackle these issues.

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Additional information

The preceding article was based on an Issue Panel presented at ISPOR 2019. For more information on the ISPOR Open-source Model Special Interest Group, go to www.ispor.org/specialinterestgroups.

Has the Time Come to Replace Randomized Controlled Trials With Real-World Evidence? A Case of Medical Devices

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On April 5, 2017, the medical devices industry welcomed a new medical device regulation (EU 2017/745) that will go into effect on May 25, 2020. The key change is strengthening the importance of clinical evidence in the regulatory process.

Medical device regulation introduced a clinical evaluation report as a framework for generating relevant information with respect to the safety and performance of medical devices, as well as its evidence on clinical benefits. The clinical evaluation report is defined as a live document with regular updates based on insights generated during day-to-day experience with a given medical device. This report is to be based on the critical evaluation of the scientific literature and real-life data collection. The medical device regulation includes postmarket clinical follow-up to ensure continuous input into a clinical evaluation report. This process is largely new for device companies and clinicians." Its objective is to routinely collect and evaluate data regarding the utilization of medical devices in real-life clinical settings.

Medical device regulation introduced a periodic safety update report for class IIa and III. In addition to postmarket clinical follow-up data, periodic safety update reports encompass postmarket surveillance as well as benefit-risk analysis. Manufacturers are also required to feed into periodic safety update reports information regarding characteristics of treated patients. For class III and implantable devices, a periodic safety evaluation report will require almost yearly updates. The compliance with medical device regulations will be vital as the periodic safety update report, along with the vigilance report and other reports, will be used to populate the European Databank of Medical Devices (Eudamed). Its key focus is market surveillance, but more detailed regulations regarding the structure of Eudamed will be defined by the end of 2019.[1]

Fulfilling requirements of the clinical evaluation report, postmarket clinical follow-up, and the periodic safety update report, which fully rely on real-world data, will not be enough. Thus, medical device regulations introduced an additional criterion of further clinical investigations, limited to the implantable and class III devices. A "clinical investigation" might be interpreted as the need for a randomized controlled trial (RCT), although this is not explicitly stated. Among the endpoints listed, there is the intended purpose, performance, safety of the device, and clinical benefit. Clinical benefits are defined very broadly as "the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcomes, including outcomes related to diagnosis, or a positive impact on patient management or public health."

Deliberation on incremental benefit or the need for a comparator control study has not been introduced." Medical device regulation does, however, mention a need for "consideration of currently available alternative treatment options for that purpose, if any."

In summary, medical device regulation has introduced multiple references to the need for real-world evidence while omitting the explicit requirement for RCTs. It provokes therefore a question about the future of RCTs in the process of medical device assessment. Can real-world evidence generation be a better choice than RCT in the evaluation of a medical device's clinical and economic benefits? There are multiple arguments that need to be weighed before any meaningful conclusions can be drawn. One can divide them into 2 groups related to pre- and postmarket launch phase.

Prelaunch Phase

Feasibility

On average, 18 months is the suggested life cycle of a medical device.[2] There are at least 2 reasons for such a short time horizon. First, medical devices can be developed for either therapeutic or diagnostic purposes, with this scope of use being changed during the clinical development. Second, unlike pharmaceuticals, medical devices are usually invented. Innovation originates

primarily from end users' insights, rather than laboratory exploration. Medical devices undergo constant "incremental" development based on clinicians' or patients' feedback. Thus, one can assume that any RCT for a medical device should take less than 2 years to complete, otherwise its results will be released when the device is already outdated. Taking into consideration the fact that the median time of a phase III trial for pharmaceuticals ranges from 3.8 to 7.2 years, the question can be asked, whether just 2 years is truly a feasible time horizon for an RCT.[3] This question relates to both efficacy (is it a sufficient follow-up period to assess treatment outcome?), as well as clinical aspects (is it a sufficient time period to assess safety of treatment?). One could allow for the evaluation of the medical device in real-life settings with the timed framework adjusted effectively to capture the full range of risks and benefits without the need for conducting RCTs.

The heterogeneity of studied patients may pose additional challenges to identify an optimal comparator. If available, one can leverage alternative data sources (such as existing registries or modeling techniques) to assess the incremental risks and benefits of given treatments against alternative treatment options. The adaptation of propensity score matching or difference-in-difference technique can ensure robust comparability of different patients' groups. Still, it does not allow for head-to-head analysis between such heterogeneous groups.

Ethics

It is a well-recognized ethical problem of placebo patients being left without active treatment. For the assessment of efficacy of medical devices, that challenge is even more profound compared to pharmaceuticals. There are some risks involved in simulating the intervention, such as anesthetic deployment and/or some surgical procedures, which may be required for both treated and placebo patients. The "standardizing" of the pre- or postoperative care of these patients can cause some disturbance as well. Blinding of participants, healthcare providers, or other caregivers in some cases may cause some risks to patients and/or be simply unrealistic. The centralized assessment of the main outcome can provide a solution, but it requires additional financial investments and tight organizational collaboration across different healthcare professionals. Real-world evidence generation is not free from ethical consideration either. Some arguments can be raised about the introduction of a new treatment prematurely before a robust level of evidence has been collected. The approach based on real-world evidence generation does mean introduction of health technology to clinical practice without the assessment of efficacy and safety on patient levels.

The clinical evaluation report is defined as a live document with regular updates based on insights generated during day-to-day experience with a given medical device.

Postlaunch Phase

End user experience

Different levels of end users' experience may lead to different levels of performance when carrying out interventions. Any RCT conducted before appropriate training and experience has been acquired, may not reflect the true clinical value of the new medical device. In such a case, an unfavorable assessment could reflect a poorly mastered technique rather than an ineffective device. One example is the analysis of 841 patients who underwent carotid endarterectomy performed by vascular or cerebrovascular neurosurgeons between January 2008 and December 2010. End users were categorized into low-volume surgeons with 40 or fewer cases per year and high-volume surgeons for higher numbers of patients treated. The complication rate of stroke and death was 6.9% for low-volume and 2.0% for high-volume surgeons (P=.001). Overall complications were 13.4% for low-volume surgeons versus high-volume surgeons 7.2% (P=.008).

The learning curve has its cost dimension as well. Another example can be the adaptation of difference-in-differences methodology to the study of total knee arthroplasties with and without bipolar sealer based on the PREMIER database in the United States. A comparison of 11,721 total knee arthroplasties and 6376 total knee arthroplasties with bipolar sealer performed in the same hospitals by surgeons with similar levels of experience in terms of number of procedures conducted in the past. The initial higher costs of bipolar sealer ($1335) were more than offset by subsequent cost savings in the second ($583) and third ($986) years post-adoption. In essence, the study provided evidence of how higher medical/surgical supplies costs can be compensated by efficiency gains such as shortened length of stay.[4]

Govindarajulu et al[5] found that learning curve models can be applied with generalized estimating equations and generalized linear mixed-effects to fit the data; however, the variability of institutional learning between different sites is likely to add to the error of most models. Overall, in the study of operator learning of a new mechanical thrombectomy device, the generalized estimating equations model tended to perform better. These models are assumed to be better applied during the vigorous initial clinical trials prior to US Food and Drug Administration approvals.[5]

To ensure an unbiased estimate of the clinical and economic benefits, it should be advisable to anticipate how long such learning phases are expected to take, and plan the timing of the assessment of a given medical device accordingly. Some examples of specific approaches for RCT can help to accommodate such challenges. An example in case can be the factorial RCT.[6,7] Since it requires a greater number of patients to be included compared to the standard randomized control study, the feasibility of such an approach may be challenging from the perspective of recruitment of study participants. The observational real-world studies on the other hand may provide more flexibility to control the impact of the end user experience. The previously mentioned difference-in-difference methodology can be a good example in case. It does, however, introduce some limitations with respect to the choice of healthcare professionals with regard to their experience with a ›

given medical device and alternative treatment options.[4]

Another issue that faces using RCT in medical device data collection, is when the clinician or the patient chooses not to participate in a new change. Equipoise may at times be the only process that justifies the test of alternative medical devices. If clinical teams believe their current medical device or technique is adequate, then they may not randomize patients to alternative strategies[12].*

Institutional Context

The clinical benefits of medical devices may be affected by the institutional factors as well. Given the fact that a result of a procedure is not only dependent on the medical device and surgical experience, but also on the complex circumstances in which the medical device is used.

The analysis of 1,377,118 patients eligible for laparoscopic abdominal surgeries in Japan between 2011 and 2013 revealed striking differences in the treatment results across more than 2000 hospitals included in the study. Not only facilities with a few cases, but also those with the highest case numbers constituted a high risk with regard to the patients' safety. It was concluded that the implementation of a new medical procedure into the clinical practice requires not only appropriate training of end users but also the implementation of safety standards.[8] Surely, it is difficult to estimate clinical benefits objectively without standardization of preoperative care (patients, hospital facilities, and equipment), perioperative care (duration of procedure, supplies), and postoperative care (assessment, follow-ups).[9] It may be even more difficult to define an appropriate comparator for the analysis. Finally, the lack of standardization of clinical care can make it challenging to define standard treatment outcome. It would be under the discretion of healthcare professionals, hence, differences across sites with respect to the reporting of treatment success.

Review of 42 studies of leadless pacemakers (pacemakers that are implanted directly into the patient's heart, avoiding the need for leads between the pacemaker and the heart, which are prone to infection) found some 2500 different individual outcomes reported.[10] It may be challenging to organize a unanimous protocol-driven RCTs if there are no standards of clinical practice across different healthcare providers utilizing the same health technology. Real-life observational study can, on the other hand, provide better understanding of suboptimalities in clinical practice and allow for evidence-based clinical guidelines generation. There are examples of such processes within the National Institute for Health and Care Excellence in the United Kingdom.[11]

Conclusions

It remains extremely challenging to define in "black or white" terms the best approach towards data collection for the assessment of new medical devices. The impact of end user experience and

Table 1. Summary of opportunities and challenges with both RCTs and RWE for medical devices.

	RCT *indicates randomized controlled trial*	**RWE** *indicates real-world evidence*
Opportunities	• Robustness in the assessment of efficacy and safety • Regime of RCT may accelerate the standardization and evidence-based utilization of medical devices in the clinical practice • Further adaptation of RCTs may increase the number of scientific publications about the value of medical devices and consequently, accelerate the uptake of innovation	• Real-life study of the benefits of medical devices provides insights into the challenges and opportunities with its use in the clinical practice • Real-life studies facilitate knowledge sharing about different methodological advancements allowing to control for end user experience • Real-life studies offer relative easiness with the engagement of healthcare providers and patients • The considerable flexibility with both retrospective and prospective real-life study framework allows for relatively easy recruitment of patients
Challenges	• Short life-cycle of medical devices provides limited time framework to study its value • Multiple devices used during a single procedure make it challenging to design an RCT that allows for assessing the efficacy of a given health technology • Ethical issues with sham comparator • Difficulties with avoiding bias of treatment effect estimation due to the learning curve effect • Lack of scientific advice, regulations and transparency on how to design RCT for a medical device. • Lack of healthcare standardization across clinical settings regarding the same health technology • Difficulties with the recruitment of homogenous patients' group (internal validity may be questionable)	• Difficulties with the assessment of the incremental value of a given medical device in cases where multiple technologies are used during a single procedure • Generalizability of study findings in the light of variety in treatment patterns across multiple healthcare providers (external validity) • Difficulties with defining an alternative treatment option for a given patient in a real-life settings • Limited possibility to study relevant endpoints in case appropriate data are not routinely collected in the clinical practice

institutional context makes it almost impossible to estimate unbiased efficacy of medical devices. One can wonder why we should search for it at all if the treatment outcome is so multidimensional in a real-life setting anyway. So far, it has been seen that real-world evidence is the more widely chosen approach for researching clinical benefits of medical devices than RCTs. Of the 215 clinical trials conducted, for 32 innovative medical devices, only 15% of them were RCTs.

There is some reluctance among healthcare professionals to study efficacy and safety of medical devices in the protocol-driven studies as well. A cross-sectional survey showed that 58% of orthopedic surgeons prefer to participate in expertise-based controlled trials compared to only 17% for conventional RCTs. Does this mean that real-world evidence will replace RCTs? The answer to that question remains unknown. It is, however, very clear that health economics and outcome research expertise is needed to guide both manufacturers and end users of medical devices in the organization of a robust approach towards data collection regarding the value of given health technology to patients, clinicians, and budget holders. The summary of opportunities and challenges with both RCTs and real-world evidence is further illustrated in Table 1.

In conclusion, it is not important which type of study framework is chosen, as long as the right research questions are posed, followed by an analysis plan that allows for appropriate information to be acquired from all potential data sources. After all, the ultimate goal is that this choice technique increases patient safety through proper scientific assessment of benefits and harms, both in the short- and long-term.

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Additional information

The preceding article was based on an issues panel presented at ISPOR 2018. To learn more about the ISPOR Special Interest Group on Medical Devices and Diagnostics, go to www.ispor.org/specialinterestgroups.

Redefining Access to Innovative Oncology Therapies: Can Managed Entry Agreements Help?

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At the ISPOR Warsaw 2019 regional conference, a panel examined country experiences with managed entry agreements and their impact on improving access to innovative oncology therapies. This article summarizes the lessons learned from implementing managed entry and multi-year, multi-indication agreements in different regional contexts.

Introduction

Delivering innovative oncology therapies to patients remains challenging in many countries, as payers and industry face pressures to ensure timely access and budget predictability while maintaining incentives for future innovation.[1] Flexible-access agreements, such as managed entry agreements (MEAs), have been identified as mechanisms for expediting patient access to innovative oncology therapies.[2] As one form of MEA, multi-year, multi-indication (MYMI) agreements present further opportunity to address the growing complexity of oncology therapies with multiple indications.

The session *Improving Patient Access to Innovative Therapies: The Role of Managed Entry Agreements* at ISPOR Warsaw 2019 examined country experiences with these agreements and their impact on improving access to innovative oncology therapies. The panel was comprised of representatives from government, the pharmaceutical industry, and patient advocacy groups, who shared their unique perspectives on how MEAs—and MYMI agreements specifically—can be used to improve patient access to innovation. This article provides an overview of lessons learned from the discussion and experiences implementing MEAs, including MYMI agreements in different country contexts.

Managed Entry Agreements Are Valuable Tools

Compared to standard procurement, MEAs have several advantages as longer-term, sustainable purchasing frameworks. These agreements distribute risks between payers and pharmaceutical companies to further their mutual goal of facilitating patient access to new medicines. Specifically, MEAs address the financial risk of overspending on new medicines above expected budgets in addition to the risk of a medicine not performing as well in real life as it did in clinical studies. Moreover, MEAs can help improve budget predictability for payers and reduce the overall administrative burden of assessing medicines, including consideration of multiple indications. In essence, MEAs enable payers to be more strategic health purchasers and generate better value for money for patients.

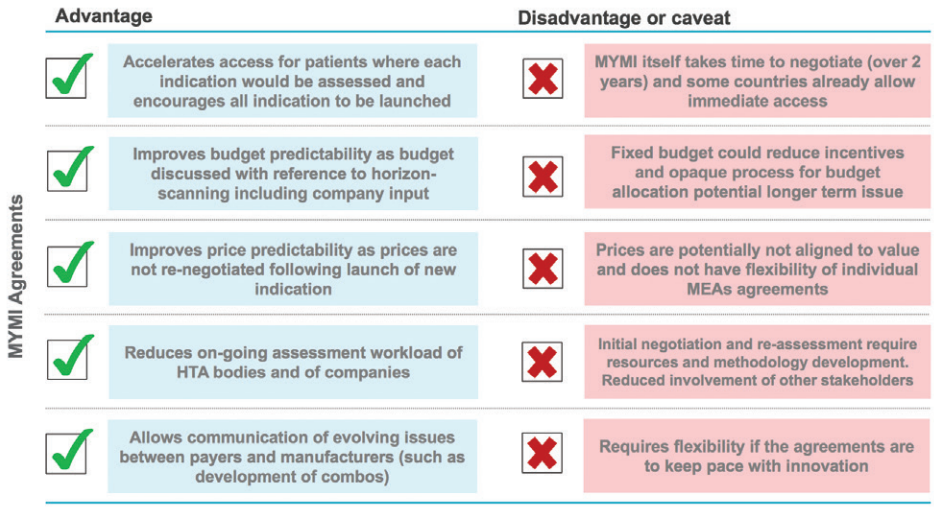
MYMI agreements are a new form of MEA between payers and manufacturers that span multiple indications and years. In the agreements of Belgium, Denmark, and the Netherlands, for example, there are light-touch or no assessments for new indications, and the price and impact on budget of new indications are discussed at the beginning of the agreement. From a theoretical perspective, MYMI agreements have several potential advantages in terms of their impact on speed of patient access, the degree to which they can help payers manage the challenges of affordability, the incentive they provide for companies to register indications, and their relative simplicity. However, it is also clear that MYMI agreements are not the only approach to providing timely patient access to pan-tumor medicines and markets which have adopted alternative approaches (eg, England's Cancer Drug Fund and immediate access in Germany where new medicines are reimbursed right after European Medicines Agency [EMA] approval with assessment one year later) should also be examined.

Strong Data Systems Support Successful Implementation of MYMI Agreements

One of the advantages of MYMI agreements is that they can reduce the administrative burden, which will be increasingly valuable given the predicted number of indications, and they can reduce the pressure on health technology assessment (HTA) agencies.

The existence of MYMI reduces the need for an assessment for every indication. While in the MYMI agreement in Belgium there is automatic coverage without any assessment, although all clinical study reports (CSRs) and economic models have to be submitted, in the Netherlands an evaluation of medical value is

Figure 1: The pros and cons of MYMI agreements – experience from Europe



undertaken, and there is a similar light touch assessment in Denmark. The latter was the case already for all hospital and oncology products and has been integrated in the MYMI agreement. It is noteworthy that even with the light touch, reimbursement can be restricted or rejected.

However, there is still a need to track usage of medicines and develop a process for assessment of the scheme. Governments should invest in strengthening data systems and use data to assess patient population sizes and complementary financing approaches. For example, Belgium is continuing to strengthen data systems and the quality of associated registries. In other cases, the data exists and just needs to be utilized. In Denmark, it was possible to leverage the existing system of patient-level health outcomes registries with the result that the system was able to track treatment performance and disease progress across the country. Showing this system of tracking patient outcomes ultimately convinced the scientific committee and the government that an MYMI agreement would be both possible and beneficial.

Legal Frameworks Need to Be Adjusted

The legal changes necessary to make MYMI possible vary from country to country. For example, previously in Belgium, it was a legal requirement that all new indications would follow the standard price and reimbursement process. While the required legal changes to support the MYMI agreement were minor, the process still took some time to agree and implement. It took a number of years to introduce the agreement, which covered a 2-year period with the option for further extensions (the current agreement expires end of 2019) applying to all I-O products and allowing new companies to be introduced into the arrangement over time.[3]

In comparison, the situation in Denmark coincided with other changes in the value assessment process, and given the company-specific nature of the contracts, did not require specific changes to rules or regulations. The disadvantage of this approach is illustrated by the Netherlands, where negotiations have been specific to each company's product and even though the Ministry of Health is familiar with the concept of a MYMI agreement (after agreeing to an initial contract with Nivolumab[4]), the negotiation process for each new product's MYMI agreement has been lengthy.

Lessons Learned From Implementation

MEAs are increasingly used tools to create budget predictability without affecting list prices.[5] Some Eastern European countries, including Croatia and Slovenia, now have over a decade of experience with MEAs, while others such as Bosnia and Herzegovina, North Macedonia, and Albania are in the initial stages of development. While not much is publicly known about MEA implementation due to confidentiality clauses, many countries appear to face similar challenges. These include establishing legal grounds to regulate MEAs and incorporate them in HTA processes, balancing decision-making transparency and the related perception of corruption, utilizing available epidemiologic data to set budget thresholds, and developing new payer competencies for negotiations with well-versed counterparts and managing the administrative workload these negotiations require.

Looking to MYMI, they can accelerate access to medicines (including indications), bringing significant benefits to patients, particularly in countries that would otherwise assess each indication. Where products would be assessed indication by indication, a process that is resource intensive and delays patient access, MYMI agreements should deliver significant benefits, as outlined in Figure 1. This accelerates patient access, meaning that greater health benefits are delivered, and incentivizes innovation. For example, in Belgium, 5,000 patients became eligible for access to immunotherapy for the lung cancer indication as a result of the MYMI agreements, with significant benefits in terms of saved lives.[5,6]

Second, MYMI agreements improve price and budget predictability. In MYMI agreements, the terms of price and budget are discussed and set based on forecasts rather than actual results, prior to the market access of new indications in the future. The application of preset prices and budgets are important as these features increase price predictability for the manufacturer and budget predictability for the payer.

Finally, MYMI agreements open a channel for the communication of evolving issues between payers and manufacturers. The experience in Belgium and the Netherlands has shown that upcoming developments—such as combination therapies—are discussed.

Although it is clear that agreements in Belgium, Denmark, and The Netherlands >

have reduced the workload and time required for the assessment of new indications, MYMI agreements generally involve a long initial negotiation between the government and the manufacturers, as there is a need to align different stakeholders.

Conclusion

To secure budget for new medicines—sometimes for treatment options that did not exist before—payers in developed countries are increasingly embracing MEAs and MYMI agreements as tools that allow them to continue providing patients with contemporary cost-effective medicines. Payers in less-developed countries are also catching up, challenged by the rising gaps in availability of innovative medicines accessible to their patients compared to those from more affluent countries.

The full potential of MEAs and MYMI agreements, however, has not been reached. The lessons learned should be shared across countries, and all countries should ensure that flexible access agreements are available as an option to expedite patient access to innovative medicines. Multistakeholder dialogues such as the session at ISPOR Warsaw are imperative forums for sharing learnings, discussing challenges, and aligning on future goals to help advance international patient access to innovative medicines.

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Q&A

Moving From Volume to Value: Humana's Approach to Addressing the Affordability Challenge

Interview With US Payer Michael Taday, PharmD, MBA, Humana

Value & Outcomes Spotlight had the opportunity to interview Michael H. Taday, PharmD, MBA, to get a payer perspective on the balance between value, access, and affordability of healthcare services. Michael is the vice president of pharmacy clinical strategies and operations at Humana, Inc, a US-based insurance company. He is considered an industry thought leader in pharmacy clinical programs, participates in multiple national advisory boards, and champions the role of the pharmacist through disruptive innovation methodologies.

Before joining Humana, Michael held various leadership roles in the pharmaceutical industry, pharmacy benefits management field, and retail pharmacy. Michael received his PharmD and MBA from the University of Maryland and a BS from the University of Arizona.

Value & Outcomes Spotlight: **Our feature article in this issue of Value & Outcomes Spotlight deals with the balance between value, access, and affordability of healthcare services. In your role at Humana, how do you mitigate affordability issues associated with high-cost and often life-saving treatments?**

Taday: Managing affordability in an age of rising healthcare costs is challenging, but increasingly important. At Humana, we've prioritized establishing affordability programs to ensure cost is not a barrier between our members and the most clinically appropriate treatment. In the past 5 years, we have launched almost a dozen programs focused on managing clinical care and affordability for prescription drugs alone. In each of these programs, we have empowered pharmacists leading clinical care teams to focus on the total cost of care and optimal outcomes.

One example is a program called ***Maximize Your Benefits.*** Through ***Maximize Your Benefits***, Humana continuously analyzes our members' prescription drug claims to identify opportunities for them to save money by switching to a lower-cost drug or by pointing them to other savings programs, such as foundation-based cost-sharing assistance. Once a savings opportunity is identified, we proactively reach out to our members and provide instructions on how to maximize their savings opportunities. We estimate that the program saved our members almost $20 million in 2018. >

Humana has also implemented interoperability tools like our real-time benefit tool (RTBT), ***IntelligentRx***, to support our members and their providers. Humana was the first Part D plan to provide real-time access to drug cost and formulary information to physicians and their patients through a RTBT. ***IntelligentRx*** enables physicians and their patients to make joint treatment decisions based upon efficacy and cost when prescribing. When presented with information on therapeutic alternatives and cost-sharing in an electronic medical record, prescribers using data from ***IntelligentRx*** switched to an alternative 37% of the time. This often results in lower out-of-pocket costs for our members and, in some cases, minimizes administrative burden for providers. The tool is currently available to 10.7 million Humana members, including individuals with Medicare, Medicaid, and employer coverage.

These are just 2 examples of how we're trying to balance the ever-increasing demands of managing the high cost of healthcare—particularly for prescription drugs—while also focusing on clinical value.

Do you see risked-sharing agreements of "pay for performance" models moving the needle on the affordability issue for US payers? What about subscription payment models?

We believe that moving from volume to value is essential to addressing affordability challenges. The traditional fee-for-service model provides misaligned incentives for everyone. We're really working to modernize payment models at Humana to decrease costs and drive towards optimal health outcomes. Currently, approximately one-third of Humana's individual Medicare Advantage members are cared for by providers in full-risk arrangements and another one-third are cared for by providers under value-based arrangements along the path of full risk. However, creating a value-centric system is not easy. One of the things we're working on is supporting providers transitioning into to risk-based arrangements. It's very different to take on risk if you have a smaller physician practice in comparison to a hospital system where there are hundreds of clinicians. One of the ways we are helping providers is with technology. By offering tools to provider clinicians with greater insights to the populations that they manage, we believe that we will create a partnership that will ultimately decrease costs and improve outcomes.

The subscription model works in very specific scenarios. The way Louisiana shaped its agreement on sofosbuvir/velpatasvir (Epclusa®) Gilead Sciences, Inc, Foster City, CA for hepatitis C for their Medicaid population is an example of where it is effective due to the size of the population and the curative nature of the drug—and we really applaud them on finding a way to make that possible. In other cases, there are lot of technical challenges to the subscription model and other longitudinal models in the prescription drug space. We've executed over 50 of these contracts, and unfortunately, outcomes-based contracts remain the exception—not the norm—and they don't produce the best arrangement in every situation. We're evaluating what we've learned from these contracts and trying to figure out the best way to apply it to future outcomes-based arrangements.

Discuss the role real-world evidence and big data are playing in informing healthcare decisions for payers.

At Humana, we fundamentally believe that every patient should be able to access, share, and control their own personal healthcare data. Providing consumers with more control over their health data will allow them to be more fully engaged in the care decision-making process—and that should occur regardless of where a patient is receiving care or who their insurance provider is. Currently, Humana supports clinicians by conducting a rich analytics review of claims to help identify opportunities for clinical interventions or when there are potential gaps in care. However, these efforts have not come without challenges. Currently, our healthcare system has inconsistent standards for clinical data sharing which makes it difficult for data to move effectively and efficiently with the patients that own that information.

The Centers for Medicare and Medicaid Services (CMS), together with its partners at the Office of the National Coordinator (ONC), has been focused on ways to minimize these challenges through new programs that encourage data sharing between beneficiaries, providers, health plans, and the government. CMS and ONC currently have a joint proposal on requiring open APIs (application programming interface) which we are really excited about and strongly support. Humana believes that open APIs and standardized data sets will be critical to unlocking the data currently captured in electronic medical records to help patients and providers with care plans regardless of the setting. CMS is also working on programs like Blue Button 2.0, which allows Medicare beneficiaries to securely share their health information with clinicians or even download it into an app on their phone, and data sharing agreements where Part D plans will receive medical data for beneficiaries to support more informed clinical decision making.

Humana is also working to expand opportunities to use data to support our members beyond what happens within our walls. In the past 6 months, we've announced 2 partnerships to increase the breadth and depth of our data use. The first is a partnership with Epic, where we will be able to tap directly into the medical record system to help improve the timeliness and accuracy of Humana-generated knowledge, ease administrative burden on providers and members, and help providers make the best decisions for patients at the point-of-care through the delivery of timely, meaningful member insights. The second partnership is with Microsoft, which will provide us with the ability to apply sophisticated analytics to our members' records and, in turn, provide clinicians and care teams with the opportunities to make a difference in patients' health.

From your vantage point, what will be the disruptive technologies or innovations that will revolutionize how we deliver and pay for healthcare in the next 10-20 years?

One of the things that we have heard loud and clear from patients is that there needs to be a shift from the traditional care settings of hospitals and nursing homes towards the home. This request is backed up with research and outcomes data proving that care in the home results in greater patient satisfaction,

makes it more likely that patients stick to their care plans, results in equal or better health outcomes, and potentially lower healthcare costs when compared to institutional settings.[1-3] One of the keys to improving the experience for our members when receiving medical care in the home will be scaling technologies that are currently in place—this will be things like remote monitoring, telehealth connections, and electronic medical records—to support patients, their caregivers, and onsite home healthcare clinicians. For example, remote monitoring can be used to collect and disseminate information to all members of a care team in real time and allow for treatment adjustments to be made if necessary. Today we have some of that functionality in place, but it has not been scaled largely, which will be essential in building the infrastructure to support the home. In addition to scaling the technology, reimbursement mechanisms will also need to evolve to allow, and even incentivize, patients to receive care in nontraditional settings. This is something that we're encouraging CMS to consider and we're currently developing models to support. We recently acquired a significant stake in Kindred at Home (the largest home health agency in the country), with the goal of bringing all of these complicated pieces together to make aging in place a reality for our members. An effective and efficient model for keeping people at home is one of our major goals as a company, and we're excited about what we can do to support our members and their families.

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