MAY/JUNE 2019 VOL. 5, NO. 3

VALUE & OUTCOMES SPOTLIGHT

An ISPOR publication for the global HEOR community

Curative Therapies:

THE NEED FOR CONSISTENT, VALIDATED, AND TRANSPARENT RECOMMENDATIONS

ALSO:

Interview with Bill Guyer

Health Technology Assessment of Curative Interventions

All data are not created equal. Understanding and predicting outcomes and costs requires specialized data.

Rheumatoid Arthritis (RA)

Heart Failure (HF)

Multiple Sclerosis (MS)

Systemic Lupus Erythematosus (SLE)

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VALUE & OUTCOMES
SPOTLIGHT

MAY/JUNE 2019
VOL. 5, NO. 3

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

ISPOR
Improving healthcare decisions

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FROM THE EDITOR

In 2014, the world of health and medicine was rocked by the introduction of Sovaldi for the treatment of hepatitis C virus. The drug evoked a broad range of extremes in response. Depending upon stakeholder perspective, it could be hailed as the poster child for medical innovation among those extolling the virtues of curative therapies, or deserving of a "Wanted, Dead or Alive" poster among those seeking to bring exorbitant drug pricing to justice.

As we have seen time and time again in the HEOR arena, the main problem is the focus on an intervention's cost as opposed to its value. A character in one of Oscar Wilde's plays once said that a cynic is someone "who knows the price of everything and the value of nothing." By this reckoning we'd have to conclude that, in the health sector, cynics abound. But how can we, as leaders in the field of HEOR, come to grips with this? Have we failed to adequately insert ourselves and our methods into the price-versus-value debate, or has the emergence of gene therapies, cancer immunotherapies, and other high-cost curative interventions exposed critical limitations in the tools and techniques of HEOR?

This issue of *Value & Outcomes Spotlight* includes a variety of contributions devoted to these themes and ties in nicely with ISPOR's flagship peer-reviewed publication, *Value in Health*, which is releasing a themed issue on health technology assessment (HTA) of curative therapies. One of our articles characterizes curative therapies as presenting new issues to old problems in HTA, while another encourages us to rethink the concept of value beyond our usual monetary metrics. We also include a Spotlight Extra discussion with Bill Guyer of Gilead Pharmaceuticals, manufacturer of Sovaldi, a by-the-numbers infographic on curative therapies (courtesy of the ISPOR Student Network), and a Q&A with Don Husereau and Shelby Reed, who were invited associate editors of the aforementioned *Value in Health* themed section.

Our ISPOR Central section contains a farewell article by outgoing ISPOR President, Federico Augustovski, in which he marks our Society's progress in promoting diversity, innovation, and influence in the healthcare realm. As ISPOR's first president from the Latin American region, Federico brought a unique perspective to the ISPOR leadership, as embodied by his famous upside-down map of the world included in his presentations at the ISPOR conferences (a portion of the map is reprinted with his piece). Speaking of Latin America, we also include a "Welcome to Bogota" article inviting you to join a thousand others at ISPOR's Latin America conference this fall—or spring, for those of you residing south of the equator!

In the meantime, this issue of *Value & Outcomes Spotlight* should reach you before the ISPOR 2019 conference in New Orleans, where if you're not careful you might find yourself needing a 'curative therapy' of sorts for the morning after every night's festivities.

See you there!

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

ISPOR SPEAKS

A Few Reflections on a Great Year: Our Progress as a Diverse, Innovative, and Influential Society

Federico Augustovski, MD, MSc, PhD, ISPOR President (2018-2019)

It has been an immense pleasure and a ´super´ enriching experience to serve as ISPOR's President this past year. I am especially proud to be completing my term as the first president that comes from "the periphery" (i.e. a country as Argentina), representing a big step for the construction of a "built-in" global view for our society. One that is less centered in the United States or Western Europe and that aims to incorporate a wide range of values and people.

THE ROAD TRAVELED

As ISPOR President, I believe I have contributed to better balancing the map, to make regions like Latin America, Asia, and Africa more prominent, helping to blend our Society with all regional cultures, values, and knowledge.

As I reflect on my term as your president, I would like to focus on our progress as a **diverse, innovative**, and **influential** Society.

DIVERSITY

ISPOR's membership increasingly reflects the collaborative research and decision-making taking place across healthcare disciplines and across borders. ISPOR promotes inclusiveness by increasing its importance and influence beyond the United States and Europe and by promoting the growth of chapters and regional consortia and networks.

The integration of different backgrounds, geographies, types of education, formative paths, experiences, and training have a significant impact in thinking and acting in a better way. We now have global voices represented in all key ISPOR Councils working to achieve our mission to promote health economics and outcomes research excellence to improve decision making for health globally. Our new governance mandates and welcomes the participation of member voices from all regions in major groups such as the Health Science and Policy Council, Health Technology Council, Global Engagement Council, Education Council, and more. The board is also working in a diversity policy to strengthen the Society's commitment to inclusion.

ISPOR continues to support HEOR advancement and utilization in low- and middle-income countries (LMIC) and committed US $2.9 million toward mission-critical initiatives in 2018 alone. The Society advances HEOR globally through worldwide conferences, training and education, and publications. It also sponsors travel grant programs for both professional and student members and funding to chapters in LMIC countries. These activities help to advance the Society's mission in emerging markets. Well over half of ISPOR's 86 regional chapters are based in LMICs, demonstrating ISPOR's commitment to advancing the use of HEOR worldwide. A new LMIC hub was put in place in our website (www.ispor.org/lmic), with a summary of benefits for members in LMICs. As a famous painter from Uruguay, I did my best to bring a different view of ISPOR, without inverting it significantly but balancing it somewhat more. (see Figure)

We also continue to explore ways to involve more mid-career people in important projects and have a thriving network for new professionals, students, and women in HEOR.

INNOVATION

ISPOR is on the forefront of high-interest and emerging areas of research that leverages technology to generate credible evidence, supporting informed healthcare decisions.

Here are just a few examples of how ISPOR is innovating and making an impact:

- ISPOR is leading discussions with many stakeholders at a time when decision making is most difficult. ISPOR hosts leading international HEOR conferences and training programs that provide unparalleled forums for education, consensus building, and networking in the field. In addition to our major conferences in Europe and North America, we hosted very successful regional events in Japan and Dubai (ISPOR's first conference held in the Middle East).

- In October of 2018 we brought together 175 HEOR expert to discuss *New Approaches to Value Assessment: Towards More Informed Pricing in Healthcare.* A series of webinars and a supplement to *Value in Health* will bring important discussions from the 2018 ISPOR Summit to the global HEOR community.

- ISPOR Good Practices for Outcomes Research reports are now required in new employee training and in decision making in industry and governments settings. In a survey of global payers last year, we learned that 84% of respondents use or find value in these reports in their work. >

- ISPOR has expanded its patient roundtables in regions including Latin America and Asia—areas where the patient voice is not so well integrated.

- *Value in Health Regional Issues*—in addition to being included in MEDLINE®—is now also indexed in Embase, Scopus, and EBSCOhost/TOC Premier. This online journal publishes research that impacts health systems in Asia; Central and Eastern Europe, Western Asia, and Africa; and Latin America.

- ISPOR continues to "speak" to the media and to thought leaders through innovative projects like the Top 10 HEOR Trends report. The 2019 report is now available at www.ispor.org/top10trends.

- ISPOR's outreach to other societies and organizations shows sincere desire to work collaboratively.

INFLUENCE

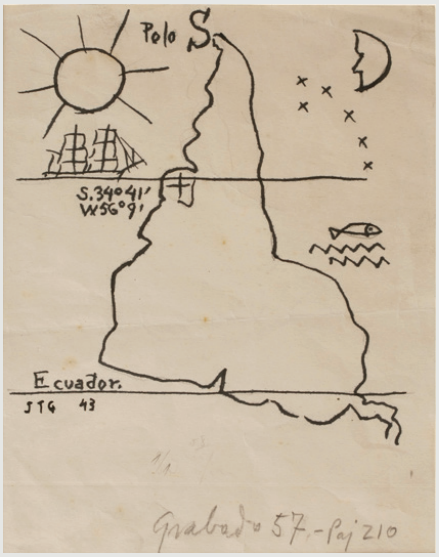
ISPOR is advancing the science of HEOR by driving consensus and uptake on good research practices across stakeholder platforms.

Never has HEOR been so needed and valuable to decision makers. The expertise within our membership is needed in all corners of the world. ISPOR now has a sophisticated mechanism in place that helps us disseminate our knowledge and resources to other stakeholders, including non-scientific parties who would benefit from ISPOR's pool of talent and expertise. Our newly reorganized website facilitates access to this wealth of information, including a new Health Technology Assessment Central portal (htacentral.org), a Patient Engagement in HEOR microsite (www.ispor.org/patient engagement); new ways for members to customize their ISPOR experience (www.ispor.org/membership) and to get involved (www.ispor.org/getinvolved).

SHOULDERS OF GIANTS

I used the famous quote about "standing on the shoulders of giants" when I began my term to refer to those who built ISPOR, an organization that is rapidly approaching a quarter century with continuous growth and success, reaching more than 20,000 members in a direct way, and influencing the work and decisions of many more. As a Society, we look to the future as we refresh our strategic plan so that together as an organization we can continue to strengthen our global impact in driving scientific and research excellence in the field of health economics and outcomes research.

Figure. América Invertida. By Joaquín Torres García



HEOR NEWS

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

1 Faced With Rising Anger on Drug Prices, Cigna Plans to Reduce Insulin Costs to $25 a Month for Many Patients (STAT)

Matthew Herper reports that in response to growing public pressure over insulin prices, Cigna and its drug benefit arm, Express Scripts. are introducing a plan to reduce the monthly cost of $40, on average, to $25 for many patients. But the new, lower price will not be available to every patient with Cigna health insurance or Express Scripts drug benefits. The announcement comes at a time when one-quarter of patients with diabetes in a study admitted to cutting back on their insulin use to reduce costs, and pharmacy benefit managers such as Express Scripts are facing congressional scrutiny.
https://www.statnews.com/2019/04/03/cigna-reduce-insulin-cost/

2 NICE Recommends Interim Funding for Lilly's Breast Cancer Drug (Pharmaphorum)

A final draft guidance from NICE has recommended interim NHS funding for Eli Lilly & Co.'s Verzenios (abemaciclib) with fulvestrant for certain breast cancer patients who previously failed on endocrine treatment. The drug will be available immediately and be reimbursed by the Cancer Drugs Fund until confirmatory cost-effectiveness data are available, NHS officials say. About 4800 women could be eligible.
https://pharmaphorum.com/news/nice-recommends-interim-funding-for-lillys-breast-cancer-drug/

3 ICER Issues Final Report on Spinraza and Zolgensma, Provides Policy Recommendations Related to Pricing and Coverage of Treatments for Spinal Muscular Atrophy (ICER)

In April, ICER released its final evidence report and report-at-a-glance assessing the comparative clinical effectiveness and value of Biogen's Spinraza (nusinersen) and Zolgensma (onasemnogene abeparvovec) from Novartis/AveXis (onasemnogene abeparvovec) for the treatment of spinal muscular atrophy (SMA). Although Spinraza and Zolgensma dramatically improve the lives of children with SMA, the current price of Spinraza "far exceeds common thresholds for cost-effectiveness," said David Rind, MD, ICER's chief medical officer. He added that while Zolgensma's price is not yet known, "There has been public discussion of prices above commonly accepted cost-effectiveness thresholds as well," and "the ripple effect of pricing decisions like these threatens the overall affordability and sustainability of the US health system." Spinraza was approved in 2016 for treating SMA in both children and adults. Zolgensma is a gene therapy that has been studied in infants with Type I SMA, and an FDA decision is expected in the first half of 2019.
https://icer-review.org/announcements/icer-issues-final-report-on-sma/

4 Reimagining Health–Flourishing (JAMA)

The April 1 issue of JAMA featured an article from Tyler J. VanderWeele, PhD, Eileen McNeely, PhD, NP1, and Howard K. Koh, MD, MPH, that discussed how standard clinical measures of health fall short of defining what patients care about more broadly—being happy and general well-being. The writers propose viewing health through the lens of "the flourishing index," which they believe has potential applications for clinical care as well as for population health. "Measurement of flourishing makes possible weighing the effects of different treatment decisions not only on physical and mental health, but in the full context of what matters in a person's life. While this makes treatment decisions more complex, it lies at the heart of patient-centered care," the writers explained.
https://jamanetwork.com/journals/jama/fullarticle/2730087?guestAccessKey=6f62a941-6bd6-4f3e-822a-8aa307e19a37&utm_source=silverchair&utm_medium=email&utm_campaign=article_alert-jama&utm_content=olf&utm_term=040119

5 Apixaban Linked to Best Outcomes in Older Patients With AFib, Heart Failure (Cardiovascular Business)

A study of Medicare patients published March 25, 2019 in PLOS One found that compared to warfarin, all direct oral anticoagulants (DOACs) were associated with fewer cardiovascular events, including heart attacks and strokes. But apixaban appeared to offer the best balance of protecting against these events while minimizing bleeding risk. The researchers used Medicare and pharmacy claims data to study thousands of patients with nonvalvular AFib (NVAF) and heart failure who filled a prescription for warfarin or a DOAC from January 2012 through September 2015. After matching 10,570 patients taking warfarin against the same number taking apixaban, researchers found those prescribed the DOAC had 36% lower odds of stroke/systemic embolism, 34% lower odds of major bleeding, and 27% lower odds of major adverse cardiovascular events (MACE).
https://www.cardiovascularbusiness.com/topics/electrophysiology-arrhythmia/apixaban-doac-choice-patients-afib-heart-failure

6 Why Are New Medicinal Products Denied Reimbursement in France? (Valid Insights)

The experts at Valid Insights look at the reasons for negative reimbursement decisions in 2017 from France's Transparency Committee. "The high proportion of products considered ineligible for reimbursement in France – after having been deemed effective and safe by the EMA – suggest early product development must be conducted with not only regulators but also payers in mind," these experts say.
https://www.validinsight.com/why-are-new-medicinal-products-denied-reimbursement-in-france/

HEOR NEWS

7 Medication Overload: America's Other Drug Problem (Lown Institute)

The Lown Institute, a nonpartisan think tank, in April released a report that concludes there is "an epidemic of too much medication" among US elderly, as more than 4 in 10 older adults take 5 or more prescription medications a day, an increase of 300% over the past 2 decades. "Over the past few decades, medication use in the United States, especially for older people, has gone far beyond necessary polypharmacy, to the point where millions are overloaded with too many prescriptions and are experiencing significant harm as a result," researchers said.

https://lowninstitute.org/wp-content/uploads/2019/04/medication-overload-lown-web.pdf

8 Parent Preferences for Health Outcomes Associated With Autism Spectrum Disorders

(Journal of Pharmaco-Economics)

Published March 21, findings from this study, conducted by Tara Lavelle of Tufts' Center for the Evaluation of Value and Risk in Health and others, suggest that autism spectrum disorder (ASD) has a significant impact on the average health utility values of children, but not of parents. However, this impact is influenced by the severity of children's core social communication and repetitive behavior symptoms. Researchers found having a child with the highest severity ASD was significantly associated with a 0.14 reduction in parent health utility (95% CI 0.01–0.26) versus the comparison group. "Although not community values, the valuations derived from these data may be useful in future CEAs of ASD interventions that demonstrate the value of interventions for ASD. As ASD interventions are aimed at symptom reduction, the utility values from this study stratified by severity level may be particularly important," these researchers say.

https://link.springer.com/article/10.1007%2Fs40273-019-00783-8#Sec19

9 ICER Appoints Dr Pamela Bradt as Chief Scientific Officer (ICER)

Pamela Bradt, MD, MPH, has been made chief scientific officer of ICER. Dr Bradt served as chief medical officer for a biopharmaceutical company focused on rare diseases. "Having worked with health technology assessment organizations around the world, I have long admired ICER's commitment to a transparent process and public forum through which all stakeholders can contribute to our understanding of a new treatment's value," said Dr Bradt. "I look forward to joining this impressive team of researchers, following where the evidence leads, and contributing to ICER's mission of helping all Americans achieve sustainable access to high-value care."

https://icer-review.org/announcements/icer_appoints_pam_bradt_cso/

10 The Relationships Between Democratic Experience, Adult Health, and Cause-Specific Mortality in 170 Countries Between 1980 and 2016: An Observational Analysis (The Lancet)

This March 13 article in The Lancet by Thomas J Bollyky, JD; Tara Templin, MS; Matthew Cohen, BS; Diana Schoder, BA; Joseph L Dieleman, PhD; and Simon Wigley, PhD looks at the association between democracy and cause-specific mortality and explores the pathways connecting democratic rule to health gains. The writers evaluated a panel of data spanning 170 countries over 26 years and found out, among other things, that increases in a country's democratic experiences were correlated with declines in mortality from cardiovascular disease and increases in government health spending.

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)30235-1/fulltext

11 People Cost Even More Than Drugs: The Imperative for Productivity (Health Affairs Blog)

Robert Kocher in the Health Affairs Blog looks at McKinsey's "The productivity imperative for healthcare delivery in the United States" and argues that healthcare costs are higher in the United States compared with other wealthy countries not because of drug prices, but the cost of highly paid people to deliver care. "Specifically, healthcare jobs are being added faster than expected based upon growth in clinical demand, and most of the new healthcare jobs are in non-valued-added job categories," Kocher says. "Fortunately, there are many things that can be done to improve labor productivity by improving clinical operations and reducing administrative complexity."

https://www.healthaffairs.org/do/10.1377/hblog20190328.816788/full/

12 Medicare for All Might Require Student Debt Relief to Work (Pacific Standard)

Although denigrated for being too expensive, some advocates have begun to point out that Medicare for All might yield savings of between $2 trillion to $5 trillion over 10 years. While some of the savings would come from curtailing the profits of health insurance and pharmaceutical companies, savings might also come from doctor pay. A relief program to get young doctors out from underneath medical school debt could prove essential in getting various physicians' groups on board with Medicare for All by taking the sting out of pay cuts.

https://psmag.com/economics/medicare-for-all-might-require-student-debt-relief-to-work

ISPOR Latin America 2019: The Leading HEOR Conference in Latin America

Yajaira Bastardo, PhD, Central University of Venezuela, Caracas, Venezuela; **Jaime Calderón, MD**, Fundación Colombiana del Corazón, Bogotá, Colombia; **Diego Rosselli, MD, MSc, MEd**, Javeriana Papal University, Bogotá, Colombia

Bastardo

Calderón

Rosselli

It is our great pleasure to invite you to ISPOR Latin America 2019, the leading health economics and outcomes research (HEOR) conference in the region, to be held 12-14 September 2019 in Bogotá, Colombia. With the theme "Data and Value in Healthcare: 2020 and Beyond," the ISPOR Latin America 2019 Conference features invited HEOR expert speakers and 2 thought-provoking plenary sessions focusing on timely, important issues facing healthcare systems across Latin America. In the first plenary, "The Role of Data Supporting an Effective Decision-Making Process," different stakeholders will explore how the management of health "data" impacts real-life healthcare decisions and resource allocation in conjunction with current trends such as digital health technologies and high-cost drugs that are disrupting traditional care and payment models across the region.

The second plenary session, "Value Measurement in 2020: Moving Forward in Low- to Middle-Income Countries," features a group of renowned panelists that will present the "value in health" perspective and discuss approaches to increase efficiency in health systems and improve access to patients.

In addition to the plenaries, the conference also includes the Short Course Program with 10 courses—3 of which are new for the region. The courses will cover topics such as budget impact analysis, introduction to real-world evidence, modeling, evaluation of medical devices, MCDA, machine learning, and more! There will also be cutting-edge issue panels, workshops, more than 450 research poster presentations, invitational meetings, ISPOR Regional Consortia meetings, and numerous special networking opportunities.

More information is available online at www.ispor.org/latinamerica2019. Be sure not to miss the early registration deadline on 30 July 2019 .

There is also a world of delights awaiting you in Bogotá. Bogotá is a spectacular cosmopolitan city with rich history and friendly people. For example, the historic neighborhood of La Candelaria is filled with interesting architecture in the old colonial style located in the center of the city. There are also many cultural museums such as the Museo del Oro (Bogotá's most famous museum) and the Museo Botero that contains sculptures, paintings, and art celebrating the works of the renowned Colombian painter and sculptor, Fernando Botero. The city offers a variety of exciting activities from cultural experiences to shopping excursions, a vibrant nightlife, and delicious traditional Colombian foods. You are sure to find the perfect activity that suits your interests.

We look forward to welcoming you in Bogotá this September to celebrate another landmark conference for ISPOR in Latin America!

CONFERENCES & EDUCATION

ISPOR Latin America 2019

Data and Value in Healthcare: 2020 and Beyond

12-14 September 2019
Bogotá, Colombia

ISPOR Latin America 2019 will center on the theme, *"Data and Value in Healthcare: 2020 and Beyond."* The conference will draw more than 1000 regional and international delegates from the HEOR community, including global leaders, policy makers, regulators, researchers, academicians, payers, patients, and patient groups. Collaborate with this multistakeholder group to share innovative research methods and health policy developments using outcomes research, patient preferences, real-world data, and clinical-, economic-, and patient-reported outcomes. The conference will feature 2 thought-provoking plenary sessions focusing on timely and important issues facing healthcare systems across Latin America.

FIRST PLENARY SESSION

The Role of Data Supporting an Effective Decision-Making Process

Real-world data extends the usefulness of randomized controlled trials by its ability to include timely data, large sample sizes that enable analysis of subpopulations and less common effects, and real-world practice and behaviors in applied research studies. Research that uses real-world data and real-world evidence are becoming increasingly important to decision makers, and through careful analysis and interpretation, this type of evidence will play an increasing role in informing healthcare decisions. In this session, stakeholders will explore how the management of these "data" impact real-life healthcare decisions and resource allocation in Latin America.

Speakers:
Bill Crown, MA, PhD, OptumLabs, USA
Rafael Alfonso, MD, MSc, PhD, GSK, USA
Oscar Espinosa, MD, MSc, Institute of Technology Assessment in Health, Colombia
Edson Amaro Jr, MD, PhD, Hospital Israelita Albert Einstein, Brazil

SECOND PLENARY SESSION

Value Measurement in 2020: Moving Forward in Low- to Middle-Income Countries

Based on the delivery model of value-based healthcare, "value" is determined by measuring health outcomes against the cost of delivering the outcomes. However, value measurement in health involves some important decisions about what to measure and how. Which key outcomes determine how the efficiency of a health system should be measured? How can the perspectives of all stakeholders be incorporated, thus making patients and providers partners in healthcare decisions? And, how can patients' access to innovation be effectively managed so that it adds value and improves health system efficiency? Panelists will present different approaches to increase efficiency in health systems and improve access to patients.

Speakers:
Alejandro Gaviria, PhD, Former Ministry of Health Colombia, Colombia
Additional speakers to be announced.
Visit www.ispor.org/LatinAmerica2019plenaries

ISPOR ESSENTIAL HEOR EDUCATION

ISPOR Short Courses kick off the conference on 12 September 2019 with 10 half- and full-day training courses designed to enhance your health economics outcomes research (HEOR) knowledge and methodologies. Learn from leading global experts and enjoy hands-on instruction on introductory through advanced topics. Apply what you learn immediately to your work and advance the science. Three exciting NEW courses this year focus on trending topics: Introduction to Real-World Evidence: Between Epidemiology and Digital Tools / Evaluation of Medical Devices: How to Manage HTAs / Introduction to Machine Learning. Register early for these and all our other popular courses; seating is limited and courses will sell out.
Learn. Apply. Advance. Come for the courses; stay for the conference!

Showcase your business as an exhibitor and with one of the many sponsorship opportunities available.
Learn more at www.ispor.org/LatinAmerica2019sponsorship

Register by 30 July 2019 and save. www.ispor.org/LatinAmerica2019reg

JOIN THE CONVERSATION ON TWITTER
#ISPORLA

CONFERENCES & EDUCATION

Mark your calendar!

ISPOR Summit 2019

October 11, 2019
Baltimore, MD, USA

Join ISPOR and prominent thought leaders in health economics and outcomes research (HEOR) and health policy for the ISPOR Summit 2019. ISPOR Summits convene a variety of healthcare stakeholders and provide a forum for discussion, exploration, and debate of critical issues in HEOR and health policy.

Save the date—October 11, 2019—and check back for additional details to follow.
Past ISPOR Summits have focused on value assessment frameworks and real-world evidence.
For a sense of what to expect, information on ISPOR Summit 2018 can be found at www.ispor.org/summit2018.

Visit www.ispor.org/summit2019 for updates

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#ISPORSummit

Highlights From ISPOR Summit 2018

New Approaches to Value Assessment: Towards More Informed Pricing in Healthcare

ISPOR hosted its third annual ISPOR Summit 2018 on October 19 in Washington, DC, USA. The event provided a forum for researchers, regulators, payers, and other stakeholders to examine the current state of healthcare value assessment and its role in pricing and coverage decisions.

ISPOR is hosting a series of webinars that highlight individual sessions presented at the Summit. In addition, *Value in Health* will publish a print supplement in June 2019 that summarizes the challenges and opportunities surrounding value frameworks, as presented from the perspective of a broad array of stakeholders.

CONFERENCES & EDUCATION

ISPOR Europe 2019

2-6 November 2019
Copenhagen, Denmark

SUBMIT YOUR ABSTRACT TODAY and share your research with this powerful group of healthcare leaders. **Abstract Submissions will remain open until 12 June**. Submit to www.ispor.org/Europe2019Submit

ISPOR Europe 2019 will feature 3 thought-provoking plenary sessions and more than 2500 presentations in the form of workshops, issue panels, forums, symposia, and podium and poster presentations on innovative research methods, health policy development using outcomes research, patient preferences, real-world data, and clinical-, economic-, and patient-reported outcomes.

The conference attracts more than 5000 stakeholders in the international HEOR community of global leaders, policy makers, regulators, researchers, academicians, payers, patients, and patient groups. This multistakeholder group is invested in using science and research to make better healthcare decisions. The diversity in work environments and international scope of attendance provide excellent networking opportunities and stimulating discussions and debate.

ISPOR ESSENTIAL HEOR EDUCATION

ISPOR Short Courses, offered in conjunction with the conference, kick off on **2 & 3 November 2019**. With **35 pre-conference Short Courses** to select from, these half- and full-day training courses are designed to enhance your knowledge and technique in 7 key topic areas relating to health economics and outcomes research and range in skill level from introductory to experienced. The courses, many of which include hands-on training, are taught by leading experts in the field.
Check out one of the 7 new courses this year!

Learn. Apply. Advance. Come for the courses; stay for the conference!

Showcase your business as an exhibitor, and with one of the many sponsorship opportunities available.
Learn more at www.ispor.org/Europe2019sponsorship

Register by 24 September and save!

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#ISPOREurope

CONFERENCES & EDUCATION

Partner with ISPOR

Renowned as the global Society that convenes all healthcare stakeholders in HEOR, ISPOR is leading the field at a time when solid approaches to decision making are more important than ever.

The Society's conference delegates, exhibitors, and sponsors participate in ISPOR's world-class, scientific conferences to network and collaborate with leading experts in HEOR around the globe.

ISPOR conferences are attended by thousands of leaders and experts representing all facets of healthcare, including researchers and academicians, regulators and assessors, decision makers, clinicians, industry, and patient representatives.

Exhibit Opportunities

Gain access to influential leaders and decision makers in HEOR by exhibiting at ISPOR's conferences. The Society's conferences draw an audience of researchers and decision makers from biopharmaceutical medical device, and diagnostics industries; payers, health ministries, government organizations, academia, and other healthcare organizations.

Sponsorship Opportunities

Increase your visibility and prominence in the field of HEOR by becoming an event sponsor. Benefits can include conference and exhibit hall registrations and highlighted listings in the exhibitor directory.

Contact us for more information or to discuss specific conference sponsorship and exhibit opportunities at sponsor@ispor.org.

ISPOR 2020 Events

ISPOR 2020
May 16-20, 2020
Orlando, FL, USA

ISPOR Asia Pacific 2020
12-15 September 2020
Seoul, South Korea

ISPOR Europe 2020
14-18 November 2020
Milan, Italy

FROM THE JOURNALS

Section Editors: **Agnes Benedict** and **Soraya Azmi**

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 as well as relevant.

Value in Health March 2019

COMPARATIVE-EFFECTIVENESS RESEARCH/HTA

Survival Extrapolation in Cancer Immunotherapy: A Validation-Based Case Study

Ash Bullement, Nicholas R. Latimer, Helen Bell Gorrod

In determining the cost-effectiveness of a novel oncology drug relative to the current standard of care (SoC), decision models have to estimate the patients' outcomes (eg, response, progression-free survival overall survival), the resulting quality of life, and the associated costs over the expected patient lifetime. However, efficacy estimates are based on data from randomized controlled trials (RCTs), which cover a much narrower time span (typically 3 to 5 years) and are often immature due to the limited number of events observed, thus requiring extrapolation.

Extrapolation is especially critical for overall survival, a key driver of cost-effectiveness. It is further complicated by the recent advancements in cancer treatment, namely immune-checkpoint inhibitors (ICIs), which may result in a proportion of patients achieving long-term survival (sometimes referred to as the "statistically cured" fraction). The accuracy of the extrapolation can be a deal-breaker for the cost-effectiveness of a therapy.

This article investigates the issue using the guidance published by the United Kingdom's National Institute for Health and Care Excellence (NICE) on the first licensed ICI ipilimumab for patients with treatment-naive advanced melanoma. Authors revisit the original assessment based on 3-years' worth of survival data using updated data (5-years' survival data) from the pivotal trial to assess the accuracy of the extrapolation methods used and to compare these to alternative extrapolation techniques with the objective of establishing whether an alternative extrapolation may have provided more accurate survival projections.

The original method used for survival extrapolation included a piecewise survival model of 3 components: (i) KM curve from a pivotal trial up to 24 months, (ii) a log-normal curve fitted to OS data over 2 to 5 years, and (iii) a Weibull curve fitted to long-term registry data. In addition, the authors also considered alternative extrapolation methods that are commonly used for oncology cost-effectiveness modelling: a standard parametric survival; a Royston and Parmar spline-based model; and mixture cure/noncure models.

All these methods are applied on 3-years' survival data, and for each method the underlying hazard function is evaluated to establish the method's applicability with respect to the observed data. The 5-years' predictions derived from each of these methods were then compared to a longer trial data-cut (5 years) while 10 to 15 years' survival prediction are compared to external real-world evidence (AJCC data) to assess clinical plausibility and validity.

Based on the initial investigation of the hazard functions estimates in the 3-year data cut, only parametric models that can accommodate increasing and then decreasing hazard were deemed appropriate. Focusing on 5-years' survival prediction, only the piecewise model and the mixture cure models (MCMs) provided estimates relatively close to the observed ones (14.4%-17.5% versus 18.1% observed).

However, the original survival piecewise predictions and MCMs diverged significantly post 5 years and remain challenging to assess which of the 2 models performs best, given that the comparability of patient characteristics between the pivotal trial and American Joint Committee on Cancer (AJCC) data is unknown. The authors concluded that only models incorporating an element of external information (through a cure fraction combined with background mortality rates or using registry data) provided accurate estimates of 5-year survival. On the contrary, flexible models that were able to capture the complex hazard functions observed during the trial, but which did not incorporate external information, extrapolated poorly.

This study is of interest to both researchers and decision makers concerned with the challenges of selecting the most appropriate survival function for therapies that have new mechanisms of action. With many options beyond the simple parametric extrapolations that were once the standard, one needs to look beyond the trial data and rely on external evidence. Although the generalizability from a single case study is difficult, this study clearly examines and details the process of survival distribution fitting and validity assessment itself. While the conclusion regarding the specific model performing best would definitely vary across individual as well as oncology indications, the steps to follow for selecting the most appropriate extrapolation will remain the same. This paper is a valuable companion in walking through the complex task of selection and shows the importance of extensive validation of survival outcome extrapolation that eventually will lead to an optimal decision regarding the adoption of new therapies.

Health Technology Assessment of Curative Interventions–an Old Problem With New Issues

Ash Bullement, BSc, MSc, Delta Hat, Nottingham, England, UK; **Anthony Hatswell, BSc, MSc**, University College London, London, England, UK; **Bonny Parkinson, BEc, MSc, PhD**, Centre for the Health Economy, Macquarie University, Sydney, NSW, Australia; **Murtuza Bharmal, BPharm, MS, PhD**, Merck Healthcare KGaA, Darmstadt, Germany

A broad range of data collection programs, methodological tools, and commercial arrangements have been proposed and adopted to inform recent health technology assessment decision making regarding such curative interventions.

Interventions with curative intent have been around for as long as evidence-based medicine and health technology assessment (HTA). The first technology appraisal conducted by the National Institute for Health and Care Excellence in the United Kingdom (UK) was on the topic of wisdom tooth extraction, and one of the first recorded randomized controlled trials (RCTs) was conducted by James Lind in 1747 regarding the consumption of citrus fruit to treat scurvy.

While early HTAs looked at similar "curative" interventions (such as different types of surgery), the term has been used (or implied) to describe a broad range of interventions that do not necessarily meet the traditional definition of a cure. Some provide patients with a "functional cure," such as emtricitabine/tenofovir (Truvada®) for human immunodeficiency virus (HIV). Others may facilitate the increased use of pre-existing curative interventions, such as brentuximab vedotin (Adcetris®), which allows an increased bridging to (curative) stem cell transplant in CD30-positive Hodgkin lymphoma. There are also some treatments which may provide durable clinical responses resulting in "long-term survivors" in indications with no precedence for such outcomes, such as axicabtagene ciloleucel (Yescarta®) for diffuse large B-cell lymphoma.

Recent developments in cancer immunotherapy, gene therapy, and novel biologics have placed pressure on HTA agencies to recommend these potentially curative interventions with uncertain long-term benefits, yet high upfront costs.

Recent developments in cancer immunotherapy, gene therapy, and novel biologics have placed pressure on HTA agencies to recommend these potentially curative interventions with uncertain long-term benefits, yet high upfront costs. The unique characteristics of these more recent interventions pose a number of difficulties in conducting HTA. This article presents a summary of key challenges, along with initiatives undertaken to address them with illustrative case studies presented.

UNCERTAINTY IN LONG-TERM CLINICAL EFFECTIVENESS

One of the common issues encountered within HTA is the uncertainty in clinical effects beyond the trial duration. While applicable to all interventions for which future benefits are anticipated, the consequences of a difference between cure or no cure has a profound impact on cost-effectiveness. Uncertainty may feature in a number of different ways—for example, uncertainty in the proportion of patients who are "cured"/"functionally cured," as well as uncertainty in the duration of the "cure-like" effect as the possibility of relapse cannot necessarily be ruled out.

To address these concerns, various initiatives have been introduced to collect further evidence—often while interventions are allocated provisional funding. In the United Kingdom, the Cancer Drugs Fund was established to defer decisions by 2 years while data are collected either regarding the use of interventions in routine clinical practice, or through extended clinical trial follow-up. In Australia, managed access programs exist where reimbursement is conditional upon the outcomes observed in real-world clinical practice. An example of this conditional reimbursement is ipilimumab (Yervoy®) for the treatment of metastatic melanoma, which was funded conditionally on 2-year overall survival (OS) in real-world clinical practice being similar to 2-year OS in the RCT.[1]

Further work is still required to establish

how best to understand (and express) the uncertainty in longer-term clinical outcomes. Real-world evidence collection efforts are becoming increasingly popular, although their collection is not always proactively undertaken in anticipation of addressing evidence gaps or enforceable by payers. There are also practical issues regarding how to proceed if the technology underperforms, resulting in payers preferring to defer funding decisions.

APPLICABILITY OF TRADITIONAL MODELLING METHODS

While the uncertainty of the clinical effect of curative interventions is a key issue in determining their likely clinical effectiveness, this issue is exacerbated further by acknowledging the array of alternative techniques that may be applied to quantify this benefit to inform cost-effectiveness analysis. Traditional curative interventions may be modelled using an explicit "cured" health state within a modelling exercise, where the term "cure" is not contested. However, the same does not necessarily apply for newer curative interventions, and so alternative methods have been utilized to inform cost-effectiveness analysis.

In the field of cancer immunotherapy, a range of methods have been proposed to extrapolate OS. These include "flexible" extrapolation functions (eg, splines) that aim to better reflect complex survival patterns versus "traditional" extrapolation functions (eg, Weibull), mixture models that aim to reflect the heterogeneity in patient populations by simultaneously modelling outcomes for 2 (or more) distinct groups, as well as extrapolation functions that involve the use of a clinically relevant landmark (such as response) to separate groups of patients by likely prognosis.[2] Each of these methods have been evaluated by HTA agencies in assessments of treatments, and are subject to limitations relating to both technical and practical issues—for instance, the plausibility of patients having a "normal" life expectancy (ie, being "cured") from baseline (as implied by some cure-based models).

To date, the primary focus of many published studies has been placed upon estimating clinical outcomes using statistical methods (as described above). However, more recently, economic model-based methods have gained popularity. These include models that incorporate health states based on response, and multistate modelling wherein individual transitions between clinically relevant health states are predicted simultaneously. Similarly, an evidence report by the Institute for Clinical and Economic Review in the United States adopted a structure wherein beyond a given point in time, patients were assumed to be effectively cured.[3] Further research is still needed to ascertain the pros and cons of adopting statistical- and/or model-based methods to best reflect outcomes associated with curative interventions. The accuracy of both approaches also needs to be demonstrated once longer-term follow-up data allow such validation.

HIGH COST OF TREATMENT

As well as the issues raised in quantifying clinical benefits, the high cost of acquisition is another common issue faced when conducting HTA of curative interventions. Interventions may be broadly categorized as those with upfront costs (such as chimeric antigen receptor T-cell [CAR-T] therapies), or those that are expected to be given repeatedly but perhaps only for a specific time period, after which the clinical effect is expected to be maintained (such as immune-checkpoint inhibitors). In both cases, however, the benefits of treatment are accrued for a much long time period versus the period over which they are paid for. The high budget impact of interventions for more common conditions constitutes a further issue in relation to patient access; a study regarding the treatment of hepatitis C in United States' prisons found that treating all inmates would have cost 13 times the overall pharmacy budget.[4]

Appropriate clinical- and cost-effectiveness assessment frameworks are of utmost importance to allow timely decision making regarding curative interventions.

Among the tools proposed to provide patient access while ensuring value for the money are risk-sharing agreements. These agreements can take many forms, broadly classified as financial-based (eg, expenditure or treatment caps) or outcomes-based (eg, only paying for cured patients). Compared to fragmented healthcare systems, such as those in the United States, these agreements have been implemented more frequently in the single-payer systems of Europe, Canada, and Australia. In the aforementioned case of ipilimumab in Australia, if there was a discrepancy between the observed versus predicted OS benefits, then the company would have to rebate the difference in costs, such that it would have been cost-effective from the date first funded.[1] However, this is an exception; despite Australia having reasonable information systems to track patient outcomes, the ability to price by indication, and the ability to enforce deals through deeds of agreement, there remains limited uptake of outcomes-based risk-sharing arrangements. This seems to be due to the administrative burden compared to expenditure caps or discounts, and for many markets outside of Australia, these administrative systems and associated policies are not yet established.

The confidential nature of many pricing arrangements between companies and payers has to date prevented detailed examination of approaches used. More transparent conceptual guidelines for acceptable pricing agreements (perhaps in the form of position statements from various payers or HTA bodies) may lead to improved access to curative interventions by finding sustainable agreements between different stakeholders.

CONCLUSIONS

The issues associated with undertaking HTA for curative interventions have existed for a very long time, although in recent history the context to which these issues apply has changed. Modern curative interventions offer previously unattainable clinical benefits to patients who would otherwise face diagnoses likely to be terminal. Appropriate clinical- and cost-effectiveness assessment frameworks are of utmost importance to allow timely decision making regarding curative interventions. >

The generation of evidence to inform HTA is constantly evolving, and decisions are increasingly being made based on maturing evidence which is often not collected within RCTs, or relies on small patient numbers (either recruited into the RCT due to biomarkers, or due to a low number with data because of administrative censoring or mortality). Increased data collection efforts are required to allow continued methodological development and the validation of proposed methods to best address the clinical- and cost-effectiveness of curative therapies. Substantial progress has been made but there is still a long way to go before we will truly be able to reliably determine the clinical- and cost-effectiveness of these newer (potentially) curative interventions and utilize appropriate payment mechanisms—by which point medical science will have inevitably advanced yet again, providing us with an entirely new set of challenges.

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By the Numbers: Curative Therapies

Section Editor: The ISPOR Student Network

Milestones in Gene Therapy

1972 First time gene therapy is suggested as treatment for genetic diseases by researchers as reported in the journal 'Science.'[1]

1990 A four-year-old girl with severe immunodeficiency became the first patient to undergo gene therapy in the United States.[2]

1999 An American patient Jesse Gelsinger dies following a gene therapy experiment, causing US regulators to put some key experiments on hold, hence pushing the field back several years.[3]

2002 Leukemia cases are diagnosed in French children undergoing gene therapy for genetic immuno-deficiency, bringing further scrutiny to the field of gene therapy.[4]

2003 The world's first gene therapy is approved in China for the treatment of head and neck cancer.[5]

2007 Doctors carry out the world's first operation using gene therapy to treat a serious sight disorder caused by a genetic defect.[6]

2012 Europe approves Glybera, the first gene therapy in a Western market, for an ultra-rare blood disorder.[7]

2016 Europe approves Strimvelis for a very rare type of immunodeficiency.[8]

2017 US-FDA approval brings first gene therapy to the United States - CAR T-cell therapy to treat certain children and young adults with B-cell acute lymphoblastic leukemia.[9]

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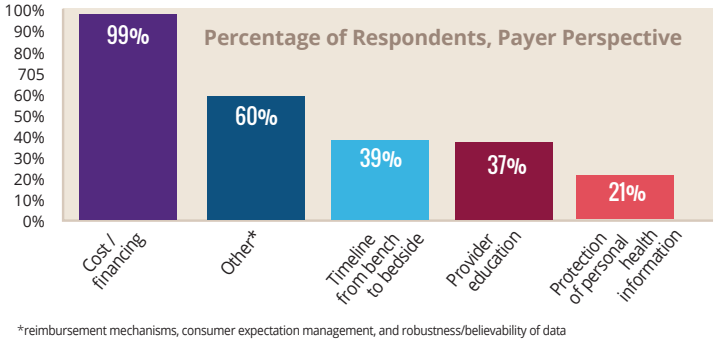
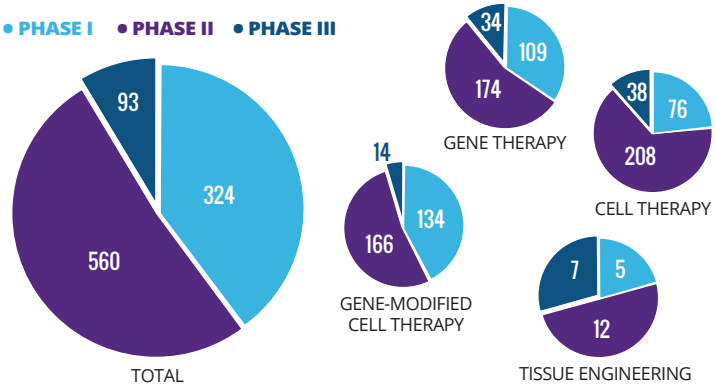
Challenges to Innovative Therapy Access[10]

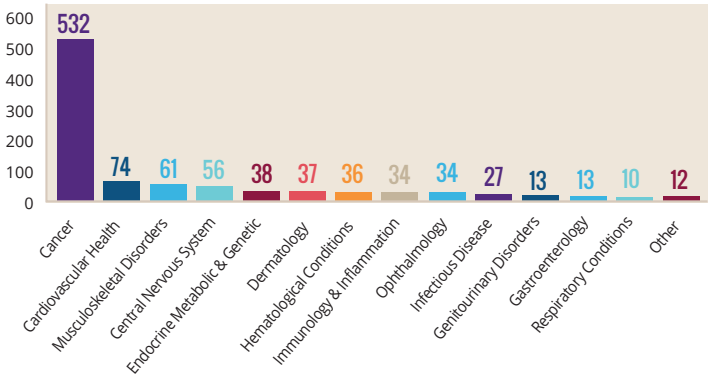


*reimbursement mechanisms, consumer expectation management, and robustness/believability of data

Number of ongoing Clinical Trials by type of Curative Therapy (as of Q2 2018)[11]



Number of ongoing Clinical Trials (CTs) by Indication (as of Q2 2018)[11]



Contributors:
Judith John, Kerala University of Health Sciences, India; Christy Choi, University of Minnesota, USA; Shannon Vaffis, University of Arizona, USA; Aakash Gandhi, University of Maryland, USA; George Okoli, University of Manitoba, Canada; Nazneen Shaikh, West Virginia University, USA; Koen Degeling, University of Twente, Netherlands; Jayesh Patel, West Virginia University, USA

Measuring Value in Healthcare Beyond Cost

Eileen Cannon, PhRMA Foundation, Washington, DC, USA

To drive healthcare reform, value assessments must be based on strong methods and patient preferences. Value varies by perspective: the concept of hope is an additional element that may be important from the patient perspective. Alternatives to the conventional QALY may be useful.

Value in health has long been equated with cost. But cost-effectiveness is just one component on the complex spectrum of value-based care. As healthcare systems and stakeholders seek to measure value in other ways, there is a need for frameworks that represent the needs and interests of decision makers.[1] Well-balanced and robust value assessment frameworks can inform decisions about a wide range of treatments with the goal of achieving better outcomes for patients.[2]

MEASURING WHAT MATTERS TO PATIENTS

Healthcare is a unique industry grappling with high consumer expectations, many diverse stakeholders, and most important, patients with distinctly different needs. Few other sectors are as vast or multifaceted. In light of this complexity, value frameworks face significant challenges, as well as substantial opportunities.

Value frameworks seek first and foremost to support decision making. However, current value assessment methods are often based on cost-utility analyses and do not always consider all factors that are of importance to patients.[3] The most comprehensive frameworks are informed by data on clinical outcomes, costs, and patient preferences. They serve a dual purpose, supporting the delivery of patient-preferred outcomes and identifying higher-cost treatments that lack a significant benefit.

Improving value assessment methodology starts with research. Leading experts are expanding traditional measurements of value to meet the needs of diverse stakeholders. While their approaches differ, 3 key principles have emerged:

- We must consider all perspectives on value: Value is in the eye of the beholder, and key aspects of value vary among patients, clinicians, payers, and society
- Value can be defined in many ways: Even within a single class of stakeholders, perspectives are often nuanced, dynamic, and heterogeneous. They are also based on clinical goals, needs, and preferences
- Alternatives to the conventional QALY may be useful: Commonly used metrics—such as the quality adjusted life-year (QALY)—may not adequately capture the full scope and meaning of value to all stakeholders

Table 1: Three Viewpoints on Value Assessment Challenges

Current Limitation	Approach to Address Limitation	Implications for Value Assessment
Varied perspectives on value may conflict with or overshadow one another	Impact analysis of various perspectives on value assessments	Greater transparency and understanding of various perspectives
Most value frameworks account only for realized or expected health outcomes, not for value of knowing, value of hope, or value of peace of mind in protection from financial catastrophe—factors that matter to patients	Discrete choice experiment to quantify value of hope	Broader value frameworks may better represent elements of importance to patients and families
Data sources and methodologies, such as QALY, may not capture all potential impacts of health interventions	Systematic review of studies and approaches that provide alternatives to QALY	Inform policy discussions about value assessment methodology and develop generic simulation tool

THREE NEW WAYS TO ASSESS HEALTHCARE VALUE

Three researchers are addressing barriers to value assessment by challenging current methodologies (Table 1).[4,5]

These scientists are specialists in health economics, outcomes research, and comparative effectiveness, and they have devoted their careers to elucidating patient-centered preferences. Gillian Sanders Schmidler, PhD, is deputy director of the Duke Margolis Center for Health Policy. Dr Schmidler has developed methods and models for evaluating the comparative effectiveness of treatments, practices, and policies. As past president of the Society for Medical Decision Making, she brings a unique patient- and-provider emphasis to the design of value assessments. She has underscored challenges in reconciling the varying and oftentimes conflicting perspectives of different stakeholders in assessing value. Shelby D. Reed, PhD, is a professor in population health sciences and medicine at the Duke Clinical Research Institute and the past president of ISPOR. As a member of 3 ISPOR task forces examining best practices for cost-effectiveness analyses, Dr. Reed has advocated for quantifying intangible but potentially meaningful aspects of value. Current value assessment frameworks fail to capture personal sources of value, such as hope, focusing largely on costs and clinical outcomes. Josh J. Carlson, PhD, an associate professor at the University of Washington, has studied uncertainty in decision-making processes and how to reduce uncertainties in real-world medical settings. In his work addressing the shortcomings of current data sources and measures designed to demonstrate value for various healthcare interventions, Dr. Carlson has also identified alternative methods for assessing value that may prove useful for healthcare decision makers. Each of these challenges and proposed solutions are described in more detail below.

EXPLORING MULTIPLE PERSPECTIVES ON VALUE

The First Panel on Cost-Effectiveness in Health and Medicine published its findings 23 years ago, recommending that analyses present their findings in a reference case that used a societal perspective. Since that time, Dr Sanders Schmidler says "many cost-effective analyses (CEA) have been performed, [but] most did not use the societal perspective, and even those that said they did often [omitted] important elements." Recognizing this critical gap, the Second Panel on Cost-Effectiveness in Health (cochaired by Dr Sanders Schmidler) recommended that CEAs report 2 reference cases—one from a healthcare sector perspective and another from a societal perspective.[6] As Dr Sanders Schmidler noted, the Second Panel was "very clear in terms of just how broad that societal perspective should be, and how it should incorporate things beyond just the normal healthcare outcomes."

One of the greatest challenges in value assessment is recognizing and interpreting different and sometimes opposing points of view. Among and between stakeholder groups, perspectives diverge on the value of specific healthcare interventions. Yet, these viewpoints are fundamental to the definitions of value that are ultimately used to select one treatment versus another. Acknowledging multiple perspectives and enhancing transparency to illustrate how framing value assessments from different perspectives may change outcomes, costs, analytic horizons, and ultimately decisions can help us develop more comprehensive, more flexible, and more inclusive value frameworks. All cost-effectiveness analyses and value assessments must be clear about which viewpoint(s) they represent and how differing viewpoints can lead to significantly different valuations.

CAPTURING THE VALUE OF HOPE

Integrating value-based care across health systems may hinge on better understanding the patient perspective. But value assessments must also consider a multitude of nuanced factors that shape and affect perceptions of value across individuals and over time. Cost and clinical benefits provide only a limited view of the scope of value, especially for patients with serious or chronic diseases. Based on discussions with cancer patients, Dr Reed is working to quantify the extent to which the value of hope represents a unique contribution to value from the patient perspective. The value of hope was explicitly recognized by ISPOR's special task force on value frameworks as one of the defining elements of value in healthcare.[7] Researchers have substantiated the significance that patients attach to hope, but the high value people assign to this outcome is frequently excluded in cost-effectiveness analyses.[8,9]

Hope can be framed as a patient's preference for a treatment that offers a chance of a significant gain *in survival* versus a treatment that offers a *certain period of survival*, even when expected survival is the same for both treatments. Knowing patients often value hope above and beyond health gains afforded by a particular treatment, value assessments that incorporate this concept may better reflect patient preferences. When asked about the value of cancer treatments, Dr Reed says many patients cite traditional measures of value, such as "length of life and quality of life. Some mention cure, being able to do what they wanted to do, playing with grandchildren, and so forth. But then a couple of [patients] simply say, 'Hope.' They just want hope."

Although patients and researchers recognize the importance of hope, this nuanced and dynamic concept can be difficult to quantify. There is also the question of whether payers should be responsible for the hope that treatments may offer patients even if they do not deliver on extending survival or improving quality of life. Nevertheless, incorporating concepts like value of hope offers payers the opportunity to view value from a more patient-centered perspective and may offer a means to better align benefit packages with patients' preferences.

EXPLORING ALTERNATIVES TO THE CONVENTIONAL QALY

The QALY is a prominent metric for capturing quantity and quality of life. QALYs are calculated by multiplying utility value by time spent in a health state and aggregating over the relevant time horizon.[10] While frequently used, the QALY has been criticized for several potential limitations. For instance, QALY calculations often assume individual patients are risk-neutral, and they may not indicate all potential impacts of healthcare interventions, eg, well-being.[11,12] Despite these critiques, use of QALYs has steadily increased, while research and implementation of strategies for overcoming the underlying flaws have lagged. >

Dr Carlson has discussed the use of QALYs and their application in decision making and value frameworks. He notes criticisms that the QALY "doesn't hold up under certain conditions" and empirical evidence that suggests "individuals are [not] risk-neutral with respect to longevity … and the sequence of health states [may] matter."

Although many objections to the QALY are well known, it remains the default measure, in part because of a perceived lack of viable alternatives. But other metrics and approaches do exist, eg, equity weighting, which Dr Carlson notes has been implemented internationally and could be evaluated for viability in the United States.[13] Another approach is expanding the QALY to include well-being.[14] These alternatives have their own sets of challenges and limitations. Further categorization of QALY alternatives can identify, examine, and compare existing gaps and uncover opportunities to ensure the underlying methods behind value assessment are accurate, precise, and meet the needs of health care stakeholders.

OVERCOMING OBSTACLES AND MOVING VALUE ASSESSMENT FORWARD

The 3 viewpoints described in this article have been endorsed by national expert-level panels, including the Second Panel on Cost-Effectiveness in Health and Medicine and ISPOR's Special Task Force on US Value Frameworks. While moving away from traditional measures of costs and benefits may seem daunting, painting a more holistic picture of value that captures the heterogeneity of patient preferences will ensure value-based care truly reflects the significance of life-saving and life-improving treatments to patients, providers, payers, and the greater public. Promoting the development of new and novel methods that address some of the widely acknowledged shortcomings of traditional value assessments will help direct scarce resources to the most effective and promising therapies.

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The Value of Transformative Therapies: An Interview with Bill Guyer

How one developer and medical educator views the shifting landscape of value frameworks.

Value & Outcomes Spotlight had the good fortune to sit down with Bill Guyer, PharmD, senior vice president of medical affairs at Gilead Sciences in Foster City, CA, USA. In his position, he oversees all therapeutic areas for approved and near-term products including: HIV, viral hepatitis, nonalcoholic steatohepatitis, hematology/oncology and inflammation for Gilead around the world. Bill is responsible for the evidence generation from the company's Global HEOR/Health Technology Assessment function. Additionally, Bill has oversight of the medical affairs function, the group at Gilead that develops and delivers medical education to healthcare practitioners, payers, patients and policy makers, as well as developing and implementing Phase 3b/4 studies for all the company's approved products. Bill also serves as secretary on the board of the Gilead Foundation, which focuses on expanding access to HIV and hepatitis education, outreach, prevention and health services. We recently spoke with Bill about how innovative technology – and curative therapies – are changing the way we think about value models in healthcare.

***VOS:* As we introduce new innovative technologies—for example cell therapy or curative therapy—is the existing health technology framework still valid?**

Bill Guyer: Current value frameworks and assessment methodology for evaluating healthcare technology have largely gone unchanged over the past 30 years, yet there have been tremendous leaps forward medically and scientifically for patients. Healthcare technology has evolved with breakthrough technologies such as cell therapy, as well as our ability to collect and analyze data, from digitized clinical trial data to real world data, that demonstrate the benefits of these breakthroughs for patients, economies, and society at large.

Value frameworks and health technology assessments would benefit from more comprehensive metrics that capture the full impact of transformative therapies. For example, appendectomies for appendicitis and direct-acting antivirals for hepatitis C provide clear-cut cures for life-threatening conditions, with clearly measurable impact on patient health. Curing an infectious disease such as hepatitis C, however, also has compounding effects, including larger public health benefits and related cost savings to healthcare systems, which should also be captured in any value assessment.

At the same time, there is a need for clearer definitions of cures, curative therapies, and products with long durations of response. Often, there may be a difference of opinion as to whether a therapy is curative before long-term follow-up is available and, in some cases, these therapies may be approved before long-term durability is known. For example, CAR Ts may be potentially curative for a subset of patients with relapsed/refractory large B-cell lymphoma based on two-year follow-up data, although additional longer term follow-up data are required to confirm. Frameworks must be designed to address this uncertainty and rapidly integrate new data, including real-world evidence, as it becomes available. This will ultimately help broaden patient access, which is, of course, the long-term goal.

For all these reasons, as health technology advances in both scope and in diversity, the older, one-size-fits-all models will need to keep pace to maximize value to patients and society.

Our current healthcare reimbursement model does not support that type of innovative, curative therapy. In your opinion what needs to be changed?

Innovation is not just about science – we must also be innovative in how we deliver and pay for medicines. Current reimbursement systems, particularly in the United States, provide little incentive for payers to recognize the full value of cures and other transformative therapies. For example, curing a life-long condition may deliver extraordinary savings in long-term healthcare costs. Yet those savings will be realized by multiple insurers over a patient's lifetime – not just the insurer that covered the one-time cure.

There's no simple solution to this challenge, but I'm encouraged that many stakeholders, both public and private, are working to develop new approaches. For example, for some therapies and conditions certain models may allow payers to address urgent medical needs while amortizing costs across multiple years. I believe there is growing consensus about the need for new models that provide access to cures while incentivizing future scientific innovation, and I am optimistic that we will see new solutions emerge in the coming years.

As we look at the evolution we are seeing in healthcare, how do we evolve to incorporate patient-centric outcomes in value assessment, rather than simply looking at health and economic outcomes?

Traditional HTA and value framework methodologies do not capture some of the most important patient outcomes, including reduction in uncertainty, insurance value of preventing conditions, such as HIV or HCV transmission, reduced severity of disease, and increased hope for the future. These important elements of patient benefit are harder to measure, but reflect how individuals, families, and society think of value.

As patients become more empowered with their healthcare choices, it's critical that we embrace patient voice in determining the relevant outcomes in clinical trial design (for example PROs to measure depression and fatigue with HCV) and the value assessment that will factor in the impact of such reduction. Patient-reported outcome measures are essential to capture the full value of transformative therapies. I hope that they will become increasingly commonplace in all healthcare settings.

An Algorithmic Approach to Optimal Study Design for HEOR and Real-World Evidence

David Thompson, PhD, Syneos Health, Manchester, MA, USA

The algorithm presented in this paper attempts to strike a practical balance between simplicity and comprehensiveness in helping steer researchers and their colleagues to appropriate research designs for outcomes research and value demonstration.

INTRODUCTION

Real-world data (RWD) and real-world evidence (RWE) are commonplace terms among health economics outcomes research (HEOR) and pharmacoepidemiology professionals, but these are now the subject of broadened interest within biopharma, medical device, and clinical research organizations. This has been fueled by a number of factors, with the December 2018 release of FDA's Real-World Evidence Program Framework likely being the most prominent reason for non-HEOR staff to hop on board the RWE bandwagon.[1]

This phenomenon presents a variety of challenges, including the need to establish agreed-upon terminology and common understanding of the available methodologic approaches for RWE generation. Most everyone within biopharma understands the tools of clinical research and the randomized controlled trial (RCT) design, but far fewer are familiar with RWD sources, methods of analyses of these, prospective approaches to RWD collection, and pragmatic clinical trials. The wider array of research methodologies can be daunting and make it difficult to find a path forward.

Health economists have faced this challenge before on a variety of fronts, including deciding on the appropriate choice of modeling approach in cost-effectiveness analysis. In these instances, algorithms have proven useful as a guide to optimal model design given the nature of the patient population, disease of interest, and treatments under consideration.[2-4]

An algorithmic approach might also be useful to provide high-level guidance on optimal study design in outcomes research and value demonstration—to date, however, no such algorithm has been provided. The purpose of this paper is to address this gap and provide a framework to facilitate discussions of real-world research design involving colleagues of varying degrees of technical expertise.

AN OVERVIEW OF THE ALGORITHM

The most frequently utilized study designs for outcomes research and value demonstration include:

- Retrospective analyses of computerized health records (administrative claims and/or electronic health records [EHRs])
- Manual chart review
- Prospective observational studies and registries
- Pragmatic trials
- Phase IV clinical trials
- Economic modeling

Confusion abounds over terminology and the wide range of research designs available for outcomes research and value demonstration.

The algorithm depicted in the figure begins at the top and systematically leads the user to one of the research designs along the bottom. It consists of a series of structured questions, most involving yes/no responses, as follows:

1) Is the study focused on an intervention?
2) If so, is the intervention on the market?
3) Are data needed for the study available from existing sources?
4) If so, are those existing sources accessible in computerized form (i.e., in administrative claims or electronic medical records [EMRs])?
5) Is the study intended to be comparative?
6) If so, is the scientific rigor of randomization needed?
7) If so, is the study setting real world?
8) If the intervention is not on the market, is the study intended to assess product value?

Responding to each of these questions within the structure of the algorithm successfully guides the researcher to 1 of 6 different research designs identified above and depicted at the bottom of the figure.

STEPPING THROUGH THE ALGORITHM

Question #1 asks whether or not the study is focused on a product. In nearly all instances, what we mean by "product" is a drug, a biologic, or a medical device. However, in some instances, the focus might be on a medical procedure, such as a surgical intervention or diagnostic test. Studies that are not product-focused will typically be disease-focused, emphasizing the following kinds of measures:

- Epidemiologic: incidence, prevalence, morbidity, mortality
- Economic: healthcare utilization, costs of care, treatment patterns
- Humanistic: disease burden, patient-reported outcomes (PROs), health-related quality of life, utilities

If the study is not product-focused, Question #3 asks whether or not data on study measures are available from existing sources. It may be that all, some, or none of the data are available from existing sources. If all or some are available from existing sources, there is potential for conducting the study as a "hybrid" retro-to-prospective data collection effort that combines different data sources, as shown in the algorithm.

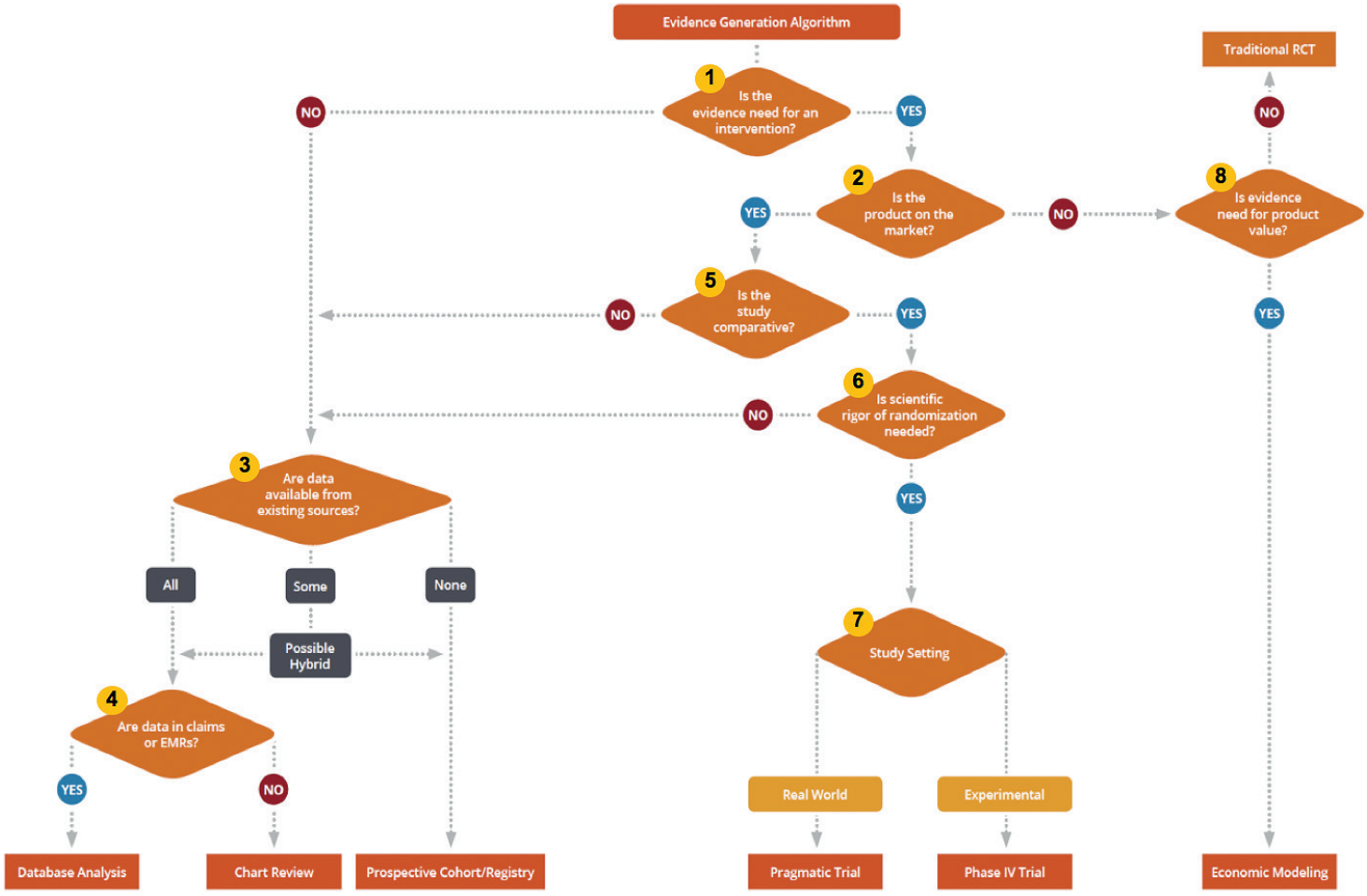
Question #4 asks whether or not the data are available in computerized form. In almost all instances, computerized data will be in the form of administrative billing claims or EMRs. If the answer is yes, then a retrospective database analysis could be performed. If the answer is no, then a manual chart review would be in order.

If none of the data are available from existing sources, or if a hybrid approach is being used, then the study would be classified as prospective observational or disease registry. From a methodologic perspective, each of these study types would be considered noninterventional, because the research does not impact the treatment decisions or care processes being observed. Regulatory classifications might differ, however.

Going back to Question #1, if the study is indeed product-focused, then Question #2 asks whether or not the product is currently on the market. This is usually a rather straightforward question to discern based on dates of regulatory approval and market launch in relation to the timing of the study.

If the product is on the market, Question #5 asks whether or not the study is comparative in nature, involving head-to-head generation of results for 2 or more interventions. In those instances where this is not obvious, a comparative analysis might be indicated by reference >

Figure. An Algorithm to Select Optimal Study Design for Outcomes Research & Value Demonstration



to such terms as:

- Comparative effectiveness analysis
- Relative effectiveness analysis
- Usual care (eg, drug A versus usual care)
- Standard care (eg, drug A versus standard care)

If the study is not comparative, the algorithm takes us back to the availability of existing data sources, Questions #3 and #4. Potential study types would then include database analyses, manual chart reviews, prospective observational, or registry. In this instance, though, it would be a product registry rather than a disease registry. Even though product-focused, all of these study types would still be considered noninterventional by methodologists. However, here too, regulatory classifications might differ.

If the study is comparative, Question #6 asks whether or not the scientific rigor of randomized treatment allocation is desired. If the answer is no, the algorithm takes us back over to the noninterventional study types and Questions #3 and #4 about suitability of existing data sources. If the answer is yes, it is necessary to assess the intended study setting to classify the study, which is the subject of Question #7.

The study setting may be experimental or real world. If real world, then the study would usually be classified as a pragmatic clinical trial, although this is somewhat of a gross simplification as there are multiple dimensions associated with the degree of trial "pragmatism."5-6 Pragmatic trials would have more-relaxed patient eligibility criteria and a less-intrusive study protocol, usually with active comparators. If experimental, then the study would usually be classified as a phase IV clinical trial. The methodologic classification for both study types is interventional.

If the product is not on the market, the study is more likely to be a phase II to III clinical trial and therefore, not in the real-world research realm. An exception occurs if the project is aimed at demonstrating product value, the possibility of which is raised by Question #8. If yes, it would be done most likely via economic modeling.

CONCLUSIONS

Current trends in the health sector have fueled broader interest in RWE generation on the part of personnel within the biopharma, medical device, and contract research industries outside of the departments of HEOR and pharmacoepidemiology. Confusion abounds over terminology and the wide range of research designs available for outcomes research and value demonstration. While algorithms are widely used to provide guidance in economic modeling and clinical decision making, no such solution exists for selecting the most appropriate real-world research design.

The above-described algorithm attempts to address this gap. Based on structured responses to a series of fairly simple questions regarding study focus and objectives, we have found through repeated use that this decision-making approach can facilitate the selection of optimal real-world research design. This algorithm may be useful to researchers, sponsors, stakeholders, and others interested in assessing alternative study designs for outcomes research and value demonstration.

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ADDITIONAL INFORMATION

The preceding article was based on a poster presented at ISPOR 2018. To view released presentations from this conference, visit the ISPOR Scientific Presentation Database at https://tools.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp.

Estimating the Costs of Adverse Events in Economic Models: Is There a "Right" Approach?

William Wong, MS, PharmD, Genentech Inc, San Francisco, CA, USA; **Josh Carlson, PhD, MPH**, University of Washington, Seattle, WA, USA; and **Martin Cloutier, MSc**, Analysis Group, Montreal, QC, Canada

There is heterogeneity in approaches to estimating the cost of adverse events for economic models with no apparent standard. Two common methods include a guidelines-based approach and claims-based approach, but potentially may provide vastly different estimates.

Estimates of adverse event (AE) costs are an important input into economic models and their inclusion has been outlined in modeling best practices guidelines such as the *ISPOR Task Force Report on Budget Impact Analyses.*[1] While the guidelines have emphasized the importance of inclusion, there has been no consensus recommendation on the most appropriate approach to estimating AE costs. The key data input needs for all estimates of AE costs include:

- Probability: Frequency of AE over a defined period
- Unit cost: Cost per episode of care associated with the event

The probability multiplied by the unit cost is the expected (average) cost per patient.

IDENTIFYING A PROBABILITY OF AN AE

The probability of an AE is commonly derived from clinical studies, where incidence is typically reported (an important assumption to note is that this assumes that the event occurred only once while under treatment). As the severity of an AE may indicate the level of resource intensity required to treat that AE, this is an important factor to consider when determining the appropriate incidence to include in a model (eg, incidence of grade 3 or 4 AEs vs incidence of any grade AEs). Furthermore, given that there can be variation in the methodology to estimate the unit cost of the adverse event, the method by which the unit cost was derived should also be considered when determining the appropriate incidence of the AE, as these should be consistent with each other (ie, if the unit cost was derived from only severe AEs, then it may be most appropriate to use the severe AE event).

Identifying the Cost of an AE: Common Limitations With Existing Literature Estimates

Sources of the unit cost may include:

- Literature
- Micro-costing approach
- Guidelines/clinical consensus-based approach
- Claims-based approach

While utilizing existing literature may be the most convenient, the objectives of AE cost studies vary and may not align with the goal of incorporation of these estimates into an economic model. Potential limitations to consider include generalizability issues, recency of the data, inclusion of treatment costs, and reporting of overall cost (rather than the incremental cost of the adverse event). Additionally, a single study may not have all adverse events required for a model, hence multiple studies with varying methodologies may be required, adding heterogeneity to the estimates.

Guidelines/Clinical Consensus-Based Approach

The guidelines/clinical consensus-based approach leverages existing clinical management guidelines and clinical expert recommendations to estimate the cost of the adverse event. Key decisions include the selection of AEs (ie, grade/severity, treatment-related, frequency above a certain threshold) and the treatment assumptions per AE (types and frequencies of medical resource utilization). There is no consensus as to which AEs to include but we suggest focusing on grade 3+ or severe AEs with a frequency above 5% for any included intervention as a good starting point, as these are most likely to require healthcare resources and have a meaningful impact on the results (note that if you include an AE for one intervention the same AEs should be included for the other interventions even if below the frequency threshold).

While the guidelines have emphasized the importance of inclusion, there has been no consensus recommendation on the most appropriate approach to estimating AE costs.

Examples of this approach using CMS physician fee schedules in oncology are given in the table below. This approach has several strengths including strong clinical validity and it is less time/resource >

intensive than some other approaches. The main limitation to this approach, however, is the potential to miss costs and the inability to account for variation in care across practices or AE management.

Grade 3/4 Toxicity	Management Assumptions	Total Cost
Fatigue	One outpatient visit ($146)	$146
Neutropenia	4 administrations of pegfilgrastim by subcutaneous injection (4 x [$4,685 + $25]) + 10% of patients have: ER visit ($176), 3-day hospital stay ($9837), primary physician consultation each day ($138 + $73 + $73), specialist visit each day (3 x $203)	$19,933
Thrombo-cytopenia	2 units of platelet transfusion ($6,427) + ER visit ($176) required 25% of time	$6472
Anemia	One outpatient visit ($146) + CBC Test ($0) + 50% of patients treated with 40,000 units of epoetin weekly for 8 weeks (20 x $30/2000 units x 8 weeks = $4800)	$2577

CLAIMS-BASED APPROACH

This data source leverages large real-world databases to estimate costs and may include multiple AEs from multiple conditions (improving consistency in estimates across AEs). This approach may entail different study designs, including a pre-defined management approach or an episode-based approach.

The predefined management approach is like that of the guidelines-based approach in that it leverages clinical expertise to define the management of the AE; however, the cost of that resource use is derived from real-world claims data (as opposed to fixed reimbursement rates for services). While this accounts for some potential variation in reimbursement rates, it may not capture the entire economic burden associated with the adverse event.

Given the differences in approaches, the estimates for a given AE may be vastly different depending on the methodology.

Alternatively, an episode-based approach attempts to capture a more holistic picture of the economic burden through matching treatment episodes with similar characteristics with and without the AE of interest. This approach allows a more comprehensive estimate of costs, including the impact that AEs may have on other conditions and increased costs in the event of multiple AEs/conditions. An additional strength is that no assumption about the AE management behavior is made.

Limitations to the claims-based approach include being limited to AEs requiring resource utilization, lack of information on the severity of an AE, and it is more time and resource intensive than the guidelines-based approach.

Example: Comparison of Estimates in Oncology

Given the differences in approaches, the estimates for a given AE may be vastly different depending on the methodology. Table 2 shows some common AEs in oncology estimated by the episode-based claims analysis approach[2] compared to the guidelines-based method (using Medicare Physician Fee Schedule, Diagnostic). While some estimates are very close, such as pneumonia or thrombocytopenia, others are vastly different such as in the case of neutropenia.

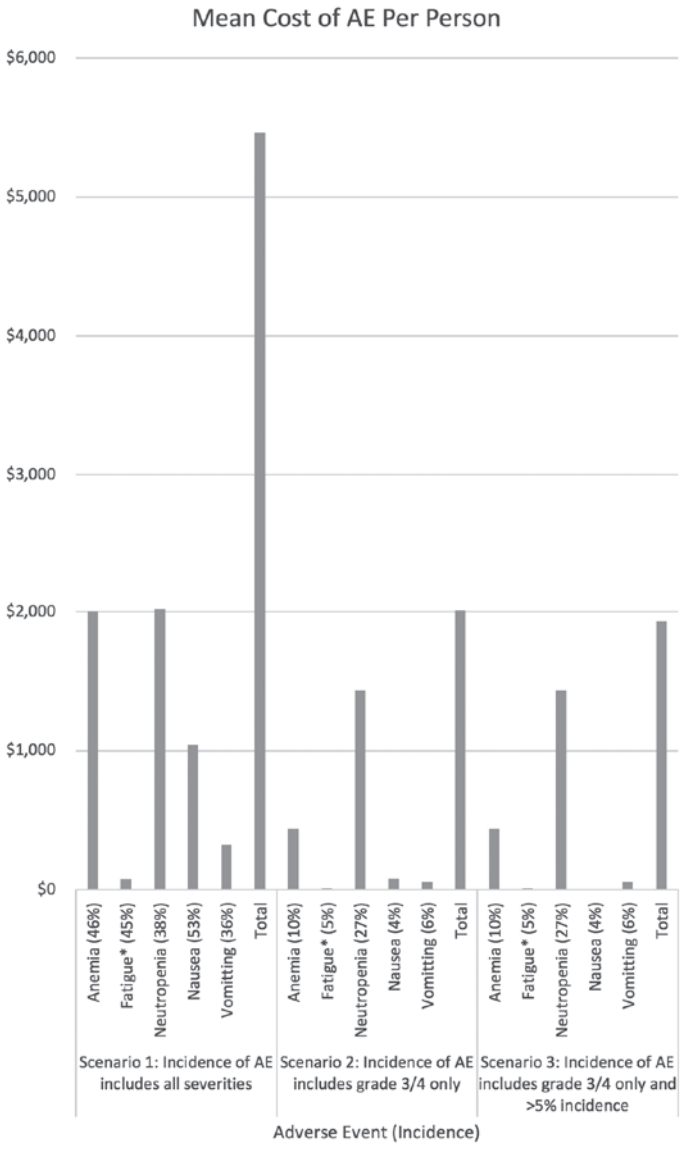
Study AE	Claims Analysis Cost (Incremental Cost per Episode)	Guidelines-Based Cost of AE	Difference
Vomiting	$895	$489	$406
Nausea	$1965	$146	$1819
Anemia	$4353	$2577	$1776
Neutropenia	$5321	$19,933	($14,612)
Thrombo-cytopenia	$6325	$6472	($147)
Pneumonia	$9941	$9808	$133
Fatigue	Not Estimated	$167	N/A

Example: Application of Estimates to Oncology Model

Adverse event cost estimates should be consistent with the AE probabilities utilized and subsequently the total costs related to AEs. When applying claims analysis-based estimates, an assumption regarding the similarity in severity of AEs observed in claims and the source of the AE rates must be made. For example, Figure 1 demonstrates how the assumption of AE severity within claims data may impact the overall costs of AEs. Given that all observed AEs in claims require resource utilization, application of claims-based estimates to all AEs regardless of severity may result in an overestimate of the AE costs that normally may be expected to be less costly, such as nausea (Figure 1: Scenario 1). Alternatively, it may be more appropriate to assume that the observed AEs are like more severe AEs, such as grade 3 or 4 in this example of oncology (Figure 1: Scenario 2). Furthermore, simplifying assumptions may be appropriate, such as utilizing an incidence rate cut-off, especially when the expected impact is minimal (Figure 1: Scenario 2 vs. Scenario 3).

When further considering the impact of these variabilities on the incremental cost-effectiveness ratio (ICER), the cost of the intervention itself is an important factor. Using the same scenarios in Figure 1, Table 3 demonstrates how the variability in intervention costs may impact the ICER. When the difference in intervention costs are small, differences in estimates of the AE costs (Scenario 1 vs 3) resulted in the largest percentage change in ICER. Conversely, large differences in intervention costs resulted in minimal impact of the ICER. These observations imply

that where interventions are costlier and hence differences in costs are potentially larger, the cost of the AEs will have less impact than when considering interventions where the AE costs are a larger proportion of the overall cost of the intervention. While this example utilizes the scenarios outlined above, similar outcomes would be expected using scenarios where different methodologies are utilized, which result in different unit costs of AEs (ie, claims-based estimates vs. guidelines-based estimates). Lastly, when examining scenario 2 vs 3, as in Figure 1, we see that simplifying assumptions may result in minimal impact, indicating that this approach potentially may be appropriate.



*For AEs with no claims data, a guidelines-based approach is used.

CONCLUSION

Guideline-based and claims-based approaches may provide different estimates of AE costs and which can potentially have a large impact on ICER estimates, depending on the circumstances. Given the strengths and limitations of both, applying a combination of both approaches may be optimal when applying estimates to economic models (ie, using a claims-based approach and supplementing with a guidelines-based approach where estimates from the claims data are not available/feasible). When choosing a method, the detail and precision needed to estimate the AE costs based on the likely impact on the outcomes of the model needs to be balanced with the effort required to estimate them accurately. In oncology models, we have found that applying claims-based estimates combined with guidelines-based estimates for AEs with a greater incidence than 5% can be a practical approach.

*Table 3: Impact of Difference in Drug Costs on Incremental Cost-Effectiveness Ratio**

	Incremental Cost-Effectiveness Ratios (ICERs)			Difference in ICER (%)	
Difference in drug costs	Scenario 1: $4268 difference in average AE costs per person[1]	Scenario 2: $1794 difference in average AE costs per person[1]	Scenario 3: $1717 difference in average AE costs per person[1]	Scenario 1 vs 3	Scenario 2 vs 3
0	$21,340	$8970	$8580	59.8	4.3
$100	$21,840	$9470	$9080	58.4	4.1
$1000	$26,340	$13,970	$13,580	48.4	2.8
$10,000	$71,340	$58,970	$58,580	17.9	0.7
$20,000	$121,340	$108,970	$108,580	10.5	0.4
$30,000	$171,340	$158,970	$158,580	7.4	0.2
$40,000	$221,340	$208,970	$208,580	5.8	0.2
$50,000	$271,340	$258,970	$258,580	4.7	0.2

*Assume difference in QALY of 0.2. ICER = (△ treatment costs + △AE costs) / (△ QALY). Example: ($100+$4268)/ (0.2) = $21,840.

[1] Assumes 50% reduction in AE incidence between treatment groups in each scenario: $\sum(probability\ of\ AE \times unit\ cost)_i - \sum(probability\ of\ AE \times 0.5 \times unit\ cost)_i$; *where i=each AE in scenario.*

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ADDITIONAL INFORMATION

The preceding article is based on a presentation from ISPOR 2018. For more information, go to https://www.ispor.org/conferences-education/conferences/past-conferences/ispor-2018.

Q&A

Extreme Remedies: Thoughts on the Future of Curative Therapies With Don Husereau, BScPharm, MSc and Shelby Reed, RPh, PhD

Value & Outcomes Spotlight had the opportunity to sit down with Don Husereau, BScPharm, MSc adjunct professor at the University of Ottawa, and Shelby Reed, RPh, PhD, professor at Duke Clinical Research Institute, to discuss the implications of emerging curative therapies for health economics outcomes research (HEOR) and the health system. Don is a past ISPOR board member, health policy consultant, and chair of the ISPOR Task Force, CHEERS (Consolidated Economic Evaluation Reporting Standards), who has previously presented and written on the Value of Cures.[1] Shelby, an ISPOR past president, is currently working on studies to evaluate patients' views on the value of potentially-curative therapies and their inclusion in value frameworks. Both played integral parts as invited associate editors, overseeing the June 2019 Curative Therapies themed section of *Value in Health*, which features 8 peer-reviewed research papers from distinguished international authors. This themed section and papers address the potential future impact of curative therapies, how global HTA bodies and payers may respond to challenges of evaluating and paying for cures, what additional factors technology assessors may need to consider, potential spillover effects from cures, and optimal models for payment.

Value & Outcomes Spotlight: **We seem to be increasingly hearing about cures, whether they are from chronic hepatitis C therapies, chimeric antigen receptor (CAR) T-cell therapies, or even curing human immunodeficiency virus (HIV) or sickle-cell disease through transplant. Is the era of cures upon us?**

Husereau: Well interestingly, that depends on how you define "cure." A number of researchers in our special issue call attention to the fact there is no standard definition for "cure." Hepatitis C has been called "curable" by the US FDA, although they are really referring to clearing virus rather than any promises of avoiding illness. The word "cure" certainly doesn't appear on the label. I think a lot of payers are skeptical of calling remedies for hepatitis C or HIV cures when there is a chance of re-infection.

Reed: One research paper in our themed section cited a 2018 study by the National Association of Managed Care Physicians and Alliance for Regenerative Medicine that made distinctions between "transformative" therapies and "curative" ones. Both terms are on a continuum with curative therapies thought to have a much longer duration of disease stabilization and no other treatment. Yet another paper that involved interviewing US payers highlighted that curative therapies imply no downstream costs. So, clinicians may have one opinion about what a cure is, but payers may have other thoughts about when to call something a "cure."

Husereau: I think many would be surprised at the pipeline for curative therapies. Another research paper in our themed section, from researchers based at the Massachusetts Institute of Technology Center for Biomedical Innovation, identified 628 gene and cellular therapies that are currently under development. Assuming similar failure rates to historical small molecules, the research team predicted that by 2030 up to 50,000 patients annually might be treated in the United States alone.

Some might argue there is nothing special about evaluating and paying for cures—that they are simply a variation of the current model of chronically treating patients; except with cures, it is one upfront treatment. Do you think that is a fair point?

Reed: It certainly may be a fair point. One could imagine a cure equivalent to the total lifetime costs and benefits of other treatments. However, cures also seem to imply a large magnitude of benefit or return to a "perfect" health state. They may also mean treatments for rare and more serious outlier conditions. Again, without a standard definition of "cure" it's hard to generalize. It's possible we may have to distinguish between

cures for specific types of diseases, like genetic diseases, or specific types of therapies, like gene therapies, that may halt disease symptoms or progression rather than using the term "cure" more broadly.

Husereau: I certainly don't get the sense that there is consensus on this point among health economists and outcomes researchers. When CAR-T emerged, there were various arguments made both for and against special value frameworks or considerations. If a cure really means an upfront treatment for rare or severe conditions, some have argued that providing robust clinical evidence is difficult (due to population sizes). But this is not often accepted by payers, who have raised concerns about single-arm trials and trials of short duration and questioned what is actually feasible in a global clinical development program. Uncertainty about durability of effect is an issue that emerges across many of the invited papers. Others have suggested there may be novel aspects of value to cures (such as spillover effects or societal preferences) that need to be addressed by HTA bodies. But it begs the question as to whether these same things might apply to other therapies. Certainly a few papers in our themed section highlight an issue that is more unique to the US—churn—paying for cures under one insurance plan, which then goes on to benefit another insurance plan when patients move, and what to do about that. Affordability is also something that all payers seem to be consistently concerned about. Apparently no one expects cures to be cheap!

So what advice then, if any, do you have for HEOR researchers who are being asked to evaluate curative therapy?

Husereau: I would say for starters, ask yourself what is meant by "curative" and whether this will be acceptable or of any relevance whatsoever to payers. Rather than focusing on the word cure, focus on what is known about the costs and benefits of treatment. Focus on what the true unmet need is. This is what payers will do.

Reed: Designs of trials, and particularly length of trials and plans for ongoing data collection will be important. How benefits are extrapolated will need to be addressed. We have already seen this to be the case with therapies like Glybera (alipogene tiparvovec), Yescarta (axicabtagene ciloleucel) and Kymriah (tisagenlecleucel). Payers will understandably be concerned about how uncertainty about the duration of effect impacts cost-effectiveness estimates. And although, as one research paper in our themed section shows, this uncertainty might optimally be addressed through outcomes-based risk-sharing arrangements, we also know that these agreements are not currently widespread. In fact, 2 other research papers describing interviews with US payers suggest these types of arrangements may not be the most desirable solution for payers due to difficulties in administration and expense.

Husereau: I think challenges with clinical evidence will remain front and center for payers. Certainly, despite analysts treating a QALY as a QALY regardless of who receives it, we know payers are likely to put some premium on treatments with a convincingly large magnitude and duration of benefit in patients with severe and debilitating conditions and for which there are no available treatments. Innovators are starting to understand that more robust evidence can have payoffs, and that starting with a thin evidence base, often to satisfy regulatory requirements and global rare-disease frameworks, can create downstream challenges for themselves along with payers.

So do we expect HTA bodies and payers to change approaches in the future era of cures?

Reed: I think it's hard to say, and a lot will also depend on whether innovators change their approaches to generating evidence beyond regulatory requirements. We know it is difficult to implement such change quickly, whether we are talking about large, global pharmaceutical companies or large private and public insurers. Until these stakeholders come together to tackle barriers to generating real-world data on relevant patient outcomes, it will be difficult to implement risk-sharing agreements. Given the stakes involved and the understanding that all stakeholders could benefit from coverage with evidence development, curative therapies might provide the tipping point.

Husereau: I think many of the lessons from funding prevention also apply to cures. I know in the Canadian province I live in, like many other jurisdictions worldwide, we have had citizens' councils saying they would put a premium on preventive therapies; however, just how much of a premium (what they would be willing to give up in treatments to receive prevention) has never been elucidated. And preventive things are often considered lower priority in reality. Another interesting aspect of cures with long-term effects is how discount rates will affect the value proposition. Cures may draw much more attention to this important aspect of research that needs to reflect societal preferences. My personal feeling is that neither HTA bodies nor innovators will make significant changes in how they approach things in the near future, despite the increasing emergence of cures. Clinical evidence will be king, as always, and therapies that fall below a threshold of credibility will simply not be funded. Similarly, companies will simply react to an austere payer environment and choose not to commercialize promising innovation, because of commercial viability. Anyway, I like saying things about the future, because I can't be wrong (at least, for now). As the old saying goes, "Prediction is difficult, especially about the future".

REFERENCE

1. Husereau D. How do we value a cure? Expert Rev Pharmacoecon Outcomes Res. 2015;15(5): 551-555.

ADDITIONAL INFORMATION

The Curative Therapies themed section will be available in the June 2019 issue of Value in Health (www.ispor.org/valueinhealth). For more information on curative therapies, visit our Personalized / Precision Medicine Special Interest Group page at www.ispor.org/specialinterestgroups. The SIG is expanding to include curative and regenerative therapies and they will have forum at ISPOR 2019 in New Orleans on Tuesday, May 21, 2019, from 12:30 to 1:45PM titled, "Leveraging Real World Evidence To Address Uncertainty For Transformative And Curative Therapies."

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505 Lawrence Square Blvd, South
Lawrenceville, NJ 08648 USA