MARCH/APRIL 2018 VOL. 4, NO. 2

VALUE & OUTCOMES SPOTLIGHT

An ISPOR publication for the global HEOR community

Evidentiary Requirements for Medical Devices

IN THIS ISSUE:

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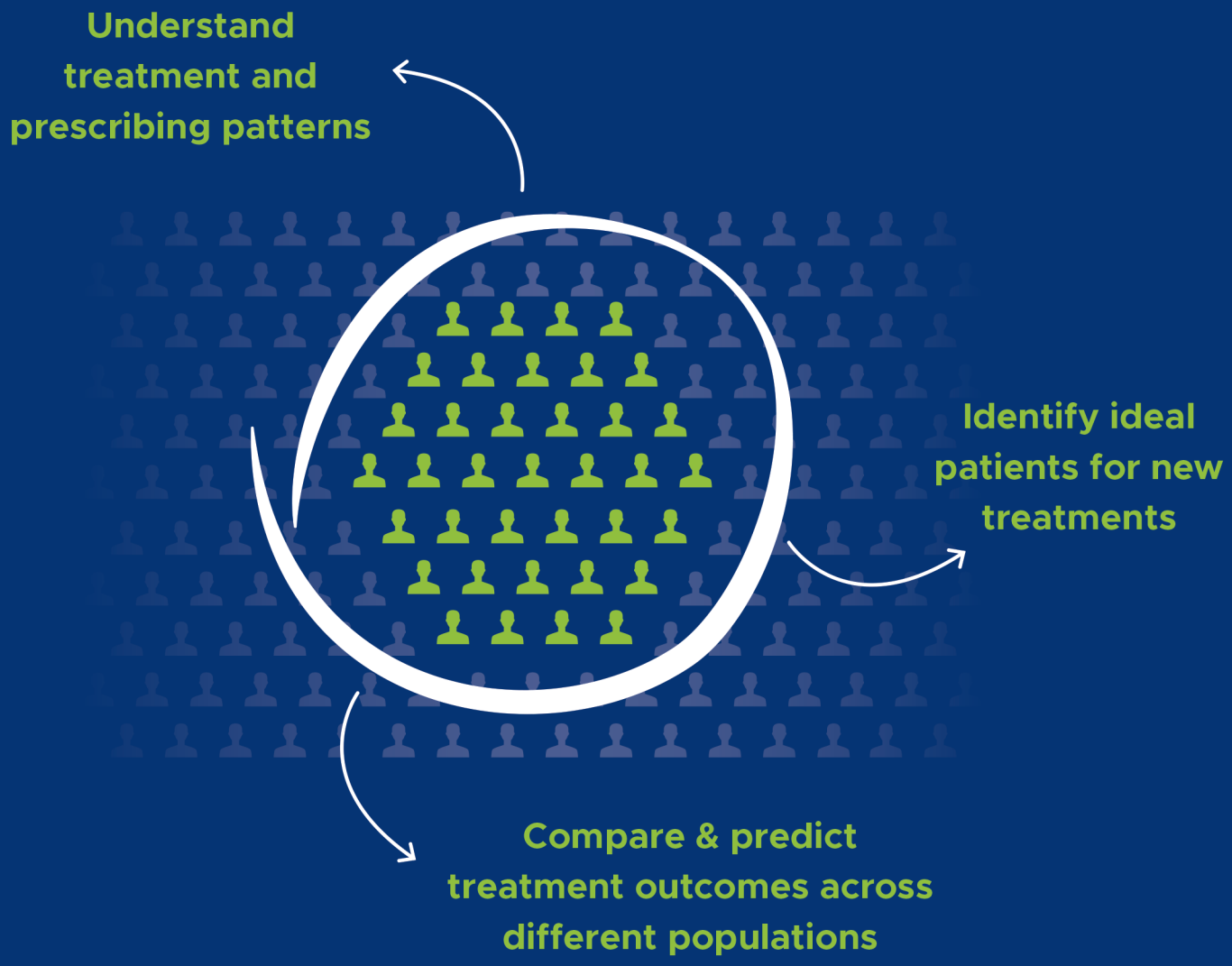

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VALUE & OUTCOMES
SPOTLIGHT

MARCH/APRIL 2018
VOL. 4, NO. 2

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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

Medical devices are widely used in the prevention, diagnosis, and treatment of disease. High-profile examples abound. In cardiology, implantable devices are used to regulate heart rhythm, prop open heart arteries, sustain heart blood flow, or when all else fails, replace the heart altogether. X-rays and other imaging technologies are used in the diagnosis of everything from ankle sprains to ankylosing spondylitis. And robotic systems are emerging that enable surgery to be performed remotely—that is, with the surgeon not even being in the operating room with the patient.

The place of medical devices in the healthcare system has some commonalities but also important differences compared with other interventions, such as pharmaceuticals. The approval process is different, with devices more commonly leveraging real-world data. Access and provision are different, with devices more often included as part of surgical procedures and less frequently dispensed by retail pharmacies. Reimbursement is different, with device costs often bundled with those of the procedure. And so on.

Importantly, these issues confer on medical devices special challenges when it comes to health technology assessment. This issue of *Value & Outcomes Spotlight* contains articles and features that bring into focus these challenges and shed light on a path forward in the context of continual change in healthcare regulation, financing, and delivery.

But that's not all. Our ISPOR Central section contains an update from ISPOR's Chief Science Officer Dick Willke on our Society's recent contributions to the debates on value assessment frameworks and real-world evidence; ten different HEOR-related news items from around the world; some relevant research published in peer-reviewed journals beyond ISPOR's *Value in Health*; and background information on upcoming ISPOR conferences, including the ISPOR 2018 conference being held in Baltimore in May.

Finally, we feature an interview with ISPOR Past-President Lou Garrison and two technical articles that will surely provoke healthy debate. The first introduces the concept of idiographic clinical trials—which apply multilevel modeling techniques to individual patient pre-test/post-test data—as an early-phase alternative to traditional randomized controlled trials. The second unpacks sources of confusion and common pitfalls in stochastic modeling studies, providing recommendations on how to avoid them.

All in all, a lot to work your way through.

Happy reading!

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

ISPOR SPEAKS

ISPOR: Extended Excellence

Richard J. Willke, PhD, ISPOR Chief Science Officer

The world is full of difficult problems and healthcare surely has its share. Being in the healthcare world, ISPOR can and should help address some of these problems. Our mission is "to promote health economics and outcomes research (HEOR) excellence to improve decision making for health globally." Promoting excellence often starts with task forces and conferences, but to get good research practices actually used in problem solving and decision making can take more than that—an extended, collaborative effort by ISPOR, our partners, and our constituencies.

Teamwork begins at home, but doesn't stop there. I've now experienced both sides of the member-staff dimension of the ISPOR team (17 years as a member, almost 2 years on staff) and have come to appreciate how well it works. The member-supplied creativity and energy is amazing when seen in all its variety, and is complemented by the staff-based structure and facilitation (and what I'd call the "flywheel" element—keeping things moving between bursts of energy). Together these efforts result in the events and HEOR products that ISPOR has become known for. Add some collaborations to this mix [eg, Society for Medical Decision Making, Academy of Managed Care Pharmacy, National Pharmaceutical Council, and International Society for Pharmacoepidemiology (ISPE)] and the potential to truly improve decision making becomes stronger yet. The challenge—and opportunity—now is to partner with other organizations not quite so steeped in our own disciplines but more proximate to broader healthcare decisions to help them understand and embrace what HEOR can bring to them. Such partnerships can also help us communicate our work outside the HEOR world per se.

> If HEOR excellence is to be leveraged to improve decision making for health, ISPOR can neither abdicate from these continued efforts nor pursue them unilaterally.

We've tackled some difficult areas, most recently with a new approach that we've called a "Special Task Force," (STF) which is a version of a task force formed for a time-sensitive, science policy-related task. In early 2016 we started the "Initiative on US Value Assessment Frameworks," involving an expert advisory panel, a stakeholder panel, and a STF of distinguished health economists co-chaired by Lou Garrison and Peter Neumann. Its work was just published in the February 2018 issue of *Value in Health*, along with 4 stakeholder commentaries. In fall 2016, we joined forces with ISPE to form a joint STF on "Real World Evidence in Health Care Decision Making," co-chaired on the ISPOR side by Marc Berger and Daniel Mullins. The task force published its reports simultaneously in *Value in Health* and *Pharmacoepidemiology and Drug Safety* (ISPE's journal) in September 2017. For each

initiative, we held a stand-alone 1-day summit in Washington, DC in order to review and discuss these efforts with participants and stakeholders.

Value assessment might be considered a fundamental activity in HEOR, and while familiar to us all, it still can be controversial in measurement and contentious in application. Controversies in measurement were deepened when several organizations came out with their own approaches to value assessment, particularly in oncology. Our health economics-oriented STF felt it was important to emphasize the importance of the conceptual underpinnings of measuring value, as well as generating research supporting the general validity of cost-effectiveness analysis (CEA) and the quality-adjusted life year (QALY) for making efficient use of healthcare resources. However, it was also necessary to recognize the need for further work in capturing some patient-centric and societal elements of value not normally measured in the QALY to help address some of its acknowledged limitations (see the paper by Lakdawalla et al in our STF report). On the application side, the contrast is even starker—practices and opinions range from using CEA exclusively in decision making to not using it at all. Our STF felt that CEA using QALY's could serve as a starting point to inform payer and policy-maker deliberations, but structured deliberative processes such as multiple criteria decision analysis should be tested and considered to allow for use of other relevant decision criteria. At ISPOR, we felt it was important to put forward a clear position on value assessment from one of our key disciplines. >

However, we readily acknowledge that it does not represent a consensus position from all of our constituencies, as is markedly demonstrated in some of the stakeholder commentaries published with the report.

Creation of real-world evidence (RWE) is another core competency in HEOR. The rapid growth of RWE available for use in decision making makes it imperative that we do the most reliable, credible, and transparent work possible. Doing so entails using both appropriate analytic methods and good procedural practices. Over the past 15 years, ISPOR Task Forces have written at least 5 reports on best practices in the use of retrospective real-world databases, focusing largely on methods that deal with data collection, data quality, and biases related to non-randomization of treatment selection. These methodological issues are difficult enough when it comes to ensuring the reliability of estimates of treatment effects. However, the credibility of RWE has also been threatened by concerns around data mining, selective reporting, and lack of replicability of results. The joint ISPOR-ISPE STF made recommendations that address these concerns in an effort to further improve study credibility and transparency in RWE evaluations.

For both value assessment and RWE areas, the STF work represents important first steps, involving collaborations with non-ISPOR researchers. The Washington DC summits were subsequent steps toward communicating beyond the research community. However, there are follow-on research topics to pursue, processes to create or support to facilitate, and decision-maker awareness and understanding to foster. If HEOR excellence is to be leveraged to improve decision making for health, ISPOR can neither abdicate from these continued efforts nor pursue them unilaterally. You can expect to see (and perhaps be involved in) further collaborations to get ISPOR's work utilized to address some of those difficult problems in healthcare.

Value in Health

Call for Papers

Back to the Future: A 20th anniversary issue of *Value in Health*

To mark *Value in Health's* 20th Anniversary, the Editors are commissioning articles for a "Back to the Future" theme that features topics that have been widely discussed in the journal over the past 20 years, but for which there is an exciting future agenda.

The themed section is tentatively scheduled to appear in the January 2019 issue of *Value in Health*. Submissions received before **August 1, 2018** have the best chance for inclusion in this themed section.

The Editors are soliciting proposals for papers and welcome suggestions on any topic, no matter how unconventional. This is the time to be creative. Potential topics for this theme might include, but are not restricted to:

- How has the definition of value in healthcare changed over the past two decades?
- How have regulatory agencies' views evolved regarding the role of regulatory bodies weighing in on value in healthcare?
- If QALYs have inadequacies, what would an alternative measure of benefit look like?
- The exponential growth in cost-effectiveness analyses suggests that their importance and impact has matured, but is there empirical evidence for that?
- How have tools and frameworks for value assessment evolved and incorporated key stakeholders' views (including patients and the public, healthcare providers and prescribers, payers and HTA organization, health policy makers, and product manufacturers)?
- If Markov models are the norm, how would we decide that we need alternative modeling approaches?
- Has the increased complexity of health economic models advanced the field by improving scientific validity or further confused decision makers?

Authors are encouraged to submit manuscripts for this themed section through our web-based tracking system at **https://mc.manuscriptcentral.com/valueinhealth**. Please indicate in your cover letter that your paper should be considered as part of this "Back to the Future" themed section.

For more information about *Value in Health* or to speak to an Editor, contact the Editorial Office.
phone: +1-609-586-4981 x130 email: viheditor@ispor.org

Value in Health Editorial Office
505 Lawrence Square Blvd South, Lawrenceville, NJ 08648 **www.ispor.org**

ISPOR
Improving healthcare decisions

HEOR NEWS

A diverse collection of relevant news briefs from the global HEOR (health economics and outcomes research) community.

1 Friction in the Path to Use of Biosimilar Drugs (NEJM)

Enactment of the Biologics Price Competition and Innovation Act (BPCIA) in 2010 raised expectations that new competition would blunt price increases for biologic drugs. The BPCIA defined an expedited pathway for biosimilars — products that are similar to and have no clinically meaningful differences from a biologic product approved by the US Food and Drug Administration— to compete with biologics that no longer have patent or regulatory market exclusivity. The expectations for increased competition were based on the experiences in Europe and estimates made by the Congressional Budget Office and private analysts. Unfortunately, the results to date are disappointing. Recently, there were only 7 biosimilar products on the US market competing with originator brands, as compared with 14 that were on the European market at a similar point in time after a pathway was created there.

http://www.nejm.org/doi/full/10.1056/NEJMp1714908?rss=searchAndBrowse&

2 FDA's Gottlieb Blames Industry 'Kabuki Drug Pricing' for High Costs (Reuters)

US Food and Drug Administration Chief Scott Gottlieb criticized pharmacy benefit managers, health insurers, and drugmakers for "Kabuki drug-pricing constructs" that profit the industry at the expense of consumers. The comments, made at a conference organized by a leading US health insurer lobbying group, stoked speculation over what steps the administration of US President Donald Trump may take to rein in lofty prescription drug costs.

https://www.reuters.com/article/us-usa-healthcare-gottlieb/fdas-gottlieb-blames-industry-kabuki-drug-pricing-for-high-costs-idUSKCN1GJ29H

3 Shifts to Generic Drugs Likely Cut Medical Costs ¥1.3 Trillion in '17: Ministry (The Japan Times)

Japan's switch to generic drugs from brand-name drugs is expected to have reduced medical costs by ¥1.3 trillion in fiscal 2017, the health ministry said. The reduction, the biggest on record, would be about 40% larger than estimated for fiscal 2015.

The ministry also said the additional premiums to keep the prices of new drugs high for specified periods of time will drop to ¥81 billion in its price revisions for fiscal 2018. The number of drugs subject to the measure will also plunge from 823 to 560.

https://www.japantimes.co.jp/news/2018/03/05/national/shifts-generic-drugs-likely-cut-medical-costs-%C2%A51-3-trillion-17-ministry/#.WqV2GIJG1Z2

4 Why Apple, Amazon, and Google Are Making Big Healthcare Moves (Vox)

Some of the biggest and most famous brands in America are making big bets on healthcare. The blue chips of Silicon Valley—Amazon, Apple, Google, Uber— have announced that they are interested in disrupting an industry that has been bedeviled by rising costs and inefficiencies for decades. It is way too early to start imagining a world where healthcare is owned by Big Tech, but something is happening here. The most proven, forward-thinking, and disruptive companies in the United States have decided that healthcare should be their next big move.

https://www.vox.com/technology/2018/3/6/17071750/amazon-health-care-apple-google-uber

5 The Deeply Human Core Of Roche's $2.1 Billion Tech Acquisition -- And Why It Made It (Forbes)

Roche's recently announced acquisition of the oncology data company Flatiron Health for $2.1 billion shows that there is significant value in a technology that can turn health data into actionable insights. According to Forbes magazine, Flatiron has created a meticulously assembled oncology dataset that pulls information from electronic health records and organizes it in a fashion that approaches the quality of clinical research, enabling investigators (and regulators) to derive insights and results from the data that might typically require a dedicated, stand-alone study.

https://www.forbes.com/sites/davidshaywitz/2018/02/18/the-deeply-human-core-of-roches-2-1b-tech-acquisition-and-why-they-did-it/#636e900129c2

6 Perspective in Economic Evaluations of Healthcare Interventions in Low- and Middle-Income Countries: One Size Does Not Fit All (Center for Global Development)

As developing nations are increasingly adopting economic evaluation as a means of informing their own investment decisions, new questions emerge. Is adopting a broader perspective to include the non-health-related benefits of healthcare interventions a wise strategy? Is it what low- and middle income countries governments want? Would it attract more internal and external funding to health? Is breaking down the funding silos—disease by disease, sector by sector—possible or even desirable? Does the choice of perspective in economic analyses matter for countries in pursuit of universal health coverage?

https://www.cgdev.org/publication/perspective-economic-evaluations-healthcare-interventions-low-and-middle-income#.WqL22aT6saU.twitter

HEOR NEWS

7 Big Pharma, Big Data: Why Drugmakers Want Our Health Records (Managed Care Magazine)

Drug-makers are racing to scoop up patient health records and strike deals with technology companies as big data analytics start to unlock a trove of information about how medicines perform in the real world, according to a Reuters report. Studying such real-world evidence offers manufacturers a powerful tool to prove the value of their drugs—something Roche aims to leverage with its recent $2 billion purchase of Flatiron Health.

http://www.managedcaremag.com/news/20180301/big-pharma-big-data-why-drugmakers-want-our-health-records

8 Irish Government Develops National Policy to Drive Biosimilar Use (Biopharma Reporter)

Ireland's National Biosimilar Medicines Policy aims to increase biosimilar use and 'drive down' the cost of medicines. At the Biopharma Ambition Conference in Dublin, minister of state of the department of health Jim Daly noted, "The government of Ireland is currently developing a national biosimilar medicines policy to promote the rational use of biosimilar medicines and to create a sustainable environment for the use of biological medicines in Ireland.

https://www.biopharma-reporter.com/Article/2018/03/06/Irish-government-develops-national-policy-to-drive-biosimilar-use?utm_source=copyright&utm_medium=OnSite&utm_campaign=copyright

9 India's Top-Selling Diabetes Drugs Backed Up by Inadequate Clinical Data (The Wire)

A new study has found that the clinical trial evidence for 5 of the most popular diabetes drug combinations in India has been inadequate. The study has been published in the British Medical Journal's 'Global Health' section. It examines the efficacy and safety of 5 of the most used metformin fixed-dose combinations in India, popularly administered for adults with type II diabetes mellitus. Metformin is a first-line treatment for diabetes. More than 60 million people in India have been diagnosed with type II diabetes mellitus.

https://thewire.in/230673/indias-top-selling-diabetes-drugs-backed-up-by-inadequate-clinical-data-study/

10 New Lehigh Valley Health Network Partnership Aims to Reduce Medical Costs by $100 Million (The Morning Call)

Lehigh Valley Health Network will pilot programs to improve care and cut costs for more than 70 health conditions in partnership with a Dublin, Ireland-based medical technology company. The 5-year agreement with Medtronic aims to reduce costs by $100 million and improve care for 500,000 Lehigh Valley Health Network patients in northeast Pennsylvania.

http://www.mcall.com/business/healthcare/mc-biz-lvhn-medtronic-20180227-story.html

RESEARCH ROUNDUP

Section Editors: **Gabriela Tannus Branco de Araujo, MSc** and **Marcelo Fonseca, MD, MSc**

Designing medical technology for resilience: integrating health economics and human factors approaches.

Borsci S, Uchegbu I, Buckle P, Ni Z, Walne S, Hanna GB.
Expert Rev Med Devices. 2018;15(1):15-26.

The adoption of innovations in medical care is still slow and faces many barriers. Limited data or information on the impact on clinical practice or perceived value perception of new technology may negatively effect the decision making process for implementation and use of a new device or diagnostic. There is a need for shared understanding of the purpose, value, and benefits provided by medical technologies to facilitate implementation.

In this study, the authors define the term resilience as "the art of managing the unexpected" or at the organizational level, "the ability to anticipate, prepare, respond and adapt." They argue that designing for resilience means designing usable and secure devices that require a minimal amount of service adaptation to allow for adoption and diffusion into various health systems, regardless of context.

To this end, the authors believe that the development of medical devices should be user-centered, which would include:

- Device design requirements and specifications;
- Stakeholder needs analysis;
- Development and assessment of user guidelines and user manuals;
- Specification of intended and abnormal use definitions;
- Risk and safety assessments;
- Interaction performance analysis (ie, understanding and predicting the learning curve and usability factors.)

The authors note that 5 health technology assessment (HTA) institutions have developed specific guidelines for evaluating medical devices, and of the 9 documents identified, 5 are specifically focused on diagnostic devices.

EUnetHTA recommends the use of cost-effectiveness or cost-utility to increase the usability of the economic evaluation, but the authors suggest another type of approach (known as HERD MedTech [Human and Economic Resilience Design for Medical Technology]) to perform these evaluations in stages prior to the development of the device.

Within the health economics and outcomes research field, the evaluation of medical and diagnostic devices still presents a challenge, mainly for the institutions that need this data to establish a rational process of decision making. In this way, formally establishing adequate parameters for the evaluation of medical devices and diagnostics is mandatory within the economic reality of health around the world. Without setting fundamental parameters, we cannot evolve into value-based healthcare.

Analysis of duplication and timing of health technology assessments on medical devices in Europe.

Hawlik K, Rummel P, Wild C.
Int J Technol Assess Health Care. 2018;34(1):18-26.

In this article, the authors discuss the methodological obstacles to performing health technology assessments (HTAs) of medical devices. Here, the EUnetHTA 2015 initiative is highlighted as a milestone in the establishment of a joint methodological framework, the HTA Core Model®, which includes a methodological guideline for the evaluation of therapeutic medical devices.

The question that motivated the authors to conduct this study was: How many evaluations of medical devices are being duplicated in Europe? To answer this question, the authors conducted a survey in the ADVANCE HTA database (HTA reports conducted by European HTA institutions as of 2004) for reports of 10 medical devices (high or medium risk) that were frequently evaluated in 2014. The study sought to estimate the level of duplication and the duration of the analysis, starting from the authorization for the medical device from January 2003 to July 2016. The study analyzed 3 primary items:

- the number of annual and global reports by technology;
- the number of evaluations per institution in the 13-year period;
- the commercialization authorization date versus the institution schedule/reporting.

The 10 medical devices analyzed in the study generated a total of 120 evaluations, and half (5) of the devices were evaluated two or more times in this period.

The authors conclude that the number of repeated analyses found in the study shows that cooperation between European HTA institutions could optimize assessments and align the used methodologies.

From the HTA technical point of view, certainly not all data is transferable from one country to another, but there is a good deal of information that can be shared. The authors' suggestion is that the adoption of a core model, such as the HTA Core Model®, could facilitate this collaboration, allowing institutions to take advantage of the exchange of valuable information.

RESEARCH ROUNDUP

Pathology and laboratory medicine in low-income and middle-income countries.

Series from the *Lancet* journals. Published online: March 15, 2018.

1. Wilson ML, Fleming KA, Kuti MA, Meng L, Lago N, Ru k. Access to pathology and laboratory medicine services: a crucial gap. Lancet. 2018. Published online: March 15, 2018.
2. Sayed S, Cherniak W, Lawler M et al. Improving pathology and laboratory medicine in low-income and middle-income countries: roadmap to solutions. Lancet. 2018. Published online: March 15, 2018.
3. Horton S, Sullivan R, Flanigan J, et al. Delivering modern, high-quality, affordable pathology and laboratory medicine to low-income and middle-income countries: a call to action. Lancet. 2018. Published online: March 15, 2018.
4. Kleinert S, Horton R. Pathology and laboratory medicine: the Cinderella of health systems.
5. Nkengasong JN, Yao K, Onyebujoh P. Laboratory medicine in low-income and middle-income countries: progress and challenges. Lancet. 2018. Published online: March 15, 2018. Lancet. 2018. Published online: March 15, 2018.
6. Citron I, Sonderman K, Meara. Pathology and laboratory medicine in partnership with global surgery: working towards universal health coverage. Lancet. 2018. Published online: March 15, 2018.
7. Watts G. Profile - Kenneth Fleming: making the global case for pathology. Lancet. 2018. Published online: March 15, 2018.

This series of 7 articles published by *The Lancet* broadly addresses access to high-quality and timely pathology and laboratory medicine (PALM) services in low-income and middle-income countries. One of the main points addressed is that sustainable development goals and universal health coverage cannot be achieved without PALM services and 4 elements were identified as barriers to the expansion of PALM access: (1) insufficient human resources and workforce capacity, (2) inadequate education and training, (3) inadequate infrastructure, and (4) insufficient quality, standards, and accreditation.

The articles also point out that information technology and point-of-care testing cannot compensate for weak healthcare systems and that there is an urgent need for more research to map the challenges of access solutions to PALM more accurately, and that if analyzed and negotiated in high volumes, diagnostic tests could be more accessible to the population.

The economic evaluations of the diagnostic devices are unique, since the diagnoses do not treat the patients directly but rather guide their treatments. Considering the therapeutic and diagnostic advances and their combination, such as personalized medicine, the challenge of extending this benefit and providing diagnosis that adds value to the health environment not only of the low-income and middle-income countries, but also of the wealthier countries represents an intellectual challenge for health economics and outcomes researchers and health technology assessment worldwide.

For those interested in evaluations that involve the use of diagnostic devices and / or focus on low-income and middle-income countries markets, we recommend reading the articles in this series online at http://www.thelancet.com/series/pathology-and-laboratory-medicine?dgcid=etoc-edschoice_email_Mar&utm_campaign=tlwglobalpath18.

CONFERENCES & EDUCATION

Next month!

ISPOR 2018

May 19-23, 2018
Baltimore Convention Center, Baltimore, MD, USA

Real-World Evidence, Digital Health, and the New Landscape for Health Decision Making

First Plenary Session: Monday, May 21, 2018 – 8:30 AM to 10:30 AM

INFLECTION POINT FOR REAL-WORLD EVIDENCE? THE TRANSFORMATIONAL ROLE OF DIGITAL HEALTH

The past 10 years has seen an exponential increase in the generation of digital health data. Additionally, traditional clinical trials are increasingly recognized as expensive, lengthy, and not adequately studying patient-specific characteristics or treatment preferences. The promise of real-world evidence is increasingly being recognized. Are we finally at the inflection point to deliver on the promises of real-world evidence and digital health? The panel of recognized leaders who are working on cutting-edge initiatives will be interviewed about what they have learned to date, current barriers to the use of real-world evidence, and what the future holds both within and outside of the United States.

Moderator: Rachael L. Fleurence, PhD; *Speakers:* Adrian F. Hernandez, MD, MHS; Danica Marinac-Dabic, MD, PhD, MMSc; Michelle McMurry-Heath, MD, PhD; Sally Okun, RN, MMHS

Second Plenary Session: Tuesday, May 22, 2018 – 8:30 AM to 10:30 AM

DIGITAL HEALTH—HELP OR HYPE?

There is increasing availability and use of digital technologies, such as smartphone apps, social media platforms, and wearables that may allow significant increases in patient participation in health-related research and general tracking of health metrics. This session will provide a balanced overview of where reliable evidence shows digital technologies have improved health and where it is mainly hype. The session will address the following questions:

- Does the empirical evidence confirm that digital health has actually improved public health?
- What evidence is there regarding the global impact of digital health on research?
- Has digital health helped to close health disparity gaps?
- What are ethical concerns surrounding tracking health data, and how are they being managed?

Moderator: C. Daniel Mullins, PhD; *Speakers:* Chris A. Jones, DPhil, MSc; Ejim E. Mark, MD, MPH, MBA; Nadia A. Sam-Agudu, MD

Third Plenary Session: Wednesday, May 23, 2018 – 10:00 AM to 11:45 AM

EXAMINING THE ROLE OF PATIENT PREFERENCES TO INFORM REGULATORY DECISIONS

The US Food and Drug Administration user fee agreements require the development of systematic approaches to collect meaningful patient input and incorporate it into regulatory review. The Center for Drug Evaluation and Research (CDER) and The Center for Devices and Radiological Health (CDRH) have taken different but complementary approaches. CDRH has concentrated on quantitative preference elicitation methods while CDER has focused on the qualitative preference elicitation methods. Preference researchers argue stated-preference studies generate valid scientific evidence on patients' views about relative desirability of harms, risks, and benefits. However, critics point out that humans rely on decision heuristics, have poor numeracy, and fail tests of internal consistency. The panel will debate the strengths and limitations of stated-preference research and the extent to which patients' views on benefit-risk tradeoffs can inform regulatory decisions.

Moderator: Shelby D. Reed, PhD; *Speakers:* Bennett Levitan, MD, PhD; Matt Reaney, FRSPH, MSc; Jeffrey Shuren, MD, JD

9 New Short Courses!

Networking Opportunities to connect and collaborate with the global HEOR community.

Online Registration closes Friday, May 18. Onsite Registration opens Saturday, May 19.

CONFERENCES & EDUCATION

ISPOR Women in Health Economics and Outcomes Research

Join us Monday, May 21, 2018 from 12:30 PM to 2:00 PM for an informative and inspirational ISPOR Women in Health Economics and Outcomes Research session at ISPOR 2018 in Baltimore, MD, USA. This event will feature special guest speaker, **Laurie Cooke**, CEO of the Healthcare Businesswomen's Association and will be led by ISPOR President **Shelby D. Reed, PhD**, Duke University, Durham, NC, USA and **Olivia Wu, PhD**, University of Glasgow, Glasgow, UK.

The vision of ISPOR's new "Women in HEOR" initiative is to support the growth, development, and contribution of women in health economics and outcomes research (HEOR); to serve as a catalyst for women's leadership in the field, and to offer a platform for ISPOR women to collaborate, network, share, and mentor each other.

This session will outline the initiative's work to date, its vision, and the business case for advancing the leadership of women in the field of HEOR. This session welcomes women and men who support the advacement of women in healthcare.

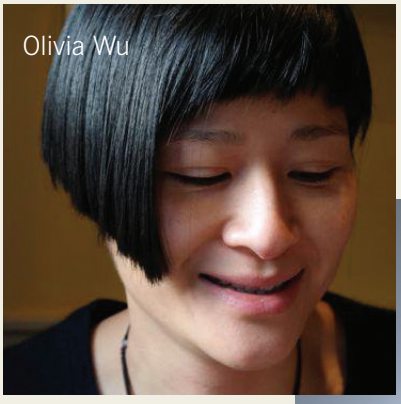
Open Meeting:

Monday, May 21, 2018 from 12:30 PM to 2:00 PM

Reception:

Monday, May 21, 2018 from 6:00 PM to 7:00 PM

Meet the Women in HEOR speakers at the ISPOR booth during the Exhibitor's Reception.


Olivia Wu


Laurie Cooke


Shelby Reed

ISPOR Asia Pacific 2018

8-11 September 2018
Tokyo, Japan

Moving Into Action: Informing Policy and Strengthening Healthcare Systems in Asia Pacific

The Conference features invited HEOR expert speakers and 3 thought-provoking plenary sessions focusing on timely and important issues facing healthcare systems across Asia Pacific.

The first plenary, ***"Transforming Healthcare and Leveraging Digital Health for Better Health in Asia Pacific,"*** explores the current challenges and possibilities in digital health in Asia Pacific, with important insight about how to grasp benefits and potential from those furthest in their digital journey.

The second plenary, ***"Real-World Evidence in Asia Pacific: Are We Ready? Is It Helpful for Decision Makers?"*** discusses the reality of real-world evidence (RWE) and its potential value, examines readiness of RWE in healthcare decision making in the region, and explores how we should approach RWE to get the most out of it. Speakers from various sectors will share their perspectives and experiences.

The third plenary, ***"Risk-Sharing Agreements: Country Experiences, Challenges, and Lessons Learned,"*** will discuss the use of risk-sharing agreements (RSAs) to manage costs, mitigate risk, and improve patient access to innovative therapies. Key issues and practical challenges in implementing RSAs will be addressed.

Anticipated: 1500 attendees • 900+ presentations • 25 exhibitors • 28 supporting institutions

New for this conference: 5 new HEOR short courses

Available now: conference and short course registration • exhibitor and sponsor opportunities

Early registration deadline: 17 July 2018

#ISPORTokyo

CONFERENCES & EDUCATION

ISPOR Dubai 2018

19-20 September 2018
Dubai, United Arab Emirates

2-day, seminar-style regional conference focusing on:

Healthcare Decision Making in the Middle East and North Africa: Role of Health Economics, Outcomes Research, and Health Technology Assessment

Featured Topics of Discussion:

Regional Middle East and North Africa (MENA) and international perspective and dialogue on:
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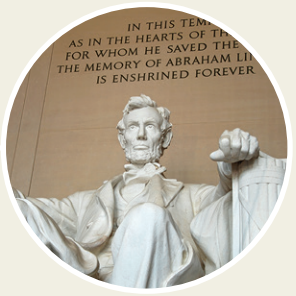

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The following Editors' Choice articles appear in the March and April 2018 issues of *Value in Health.*

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March 2018

THEMED SECTION: AFFORDABILITY IN HEALTHCARE

The March 2018 issue features a themed section on the affordability of health technologies, edited by Josephine Mauskopf and Adrian Towse. This themed section includes 3 articles and 2 commentaries that examine the issue of afordability from different persepectives.

Editorial

Affordability of New Technologies: The Next Frontier

Adrian Towse, Josephine Mauskopf

Articles

Affordability Challenges to Value-Based Pricing: Mass Diseases, Orphan Diseases, and Cures

Patricia M. Danzon

The ICER Value Framework: Integrating Cost Effectiveness and Affordability in the Assessment of Healthcare Value

Steven D. Pearson

Resolving the 'Cost Effective but Unaffordable' 'Paradox': Estimating the Health Opportunity Costs of Non-Marginal Budget Impacts

James Richard Scott Lomas, Karl Claxton, Stephen Martin, and Marta Soares

Commentaries

Paying for Cures: Perspectives on Solutions to the "Affordability Issue"

Sarah Karlsberg Schaffer, Donna Messner, Jorge Mestre-Ferrandiz, Ellen Tambur, and Adrian Towse

Affordability of Healthcare: A Global Crisis

John B. Watkins

ECONOMIC EVALUATION

Estimating the Learning Curve of a Novel Medical Device: Bipolar Sealer Use in Unilateral Total Knee Arthroplasties

Victoria Kuznietsova and Robert S. Woodward

The authors estimate the learning curve for a novel medical device.

HEALTH POLICY ANALYSIS

Real-World Evidence: Useful in the Real World of United States Payer Decision Making. How? When? and What Studies?

Daniel C. Malone, Mary Brown, Jason T. Hurwitz, Jennifer Graff, and Loretta Peters

The authors explore US payers' perceptions of the current use and value of real world evidence.

April 2018

THEMED SECTION: PhRMA FOUNDATION CHALLENGE AWARDS

In 2017, the PhRMA Foundation introduced a value assessment challenge award that posed the question: What are transformative strategies to measure the value of healthcare interventions? This themed section includes the 3 top challenge-winning papers and each one views value through a different lens.

Editorial

The Value Challenge: Examining the Transformative Strategies to Measure or Evaluate the Value of Healthcare Interventions

Bryan R. Luce

Articles

A Framework for Measuring Low-Value Care

George Miller, Corwin Rhyan, Beth Beaudin-Seiler, Paul Hughes-Cromwick

Improving Value for Eczema Patients

Julie Block

Emerging Good Practices for Transforming Value Assessment: Patients' Voices, Patients' Values

Jason Harris, Eleanor M. Perfetto, C. Daniel Mullins, Susan dosReis

ECONOMIC EVALUATION

Cost-Effectiveness of Take-Home Naloxone for the Prevention of Fatalities of Heroin Overdose

Sue Langham, Antony Wright, James Kenworthy, Richard Grieve, William Dunlop

The authors assess the cost-effectiveness of distributing naloxone to adults at risk of heroin overdose for use by nonmedical responders compared with no naloxone distribution in a European healthcare setting.

SYSTEMATIC REVIEWS

Utility-Based Instruments for People With Dementia: A Systematic Review and Meta-Regression Analysis

Li Li, Kim-Huong Nguyen, Tracy Comans, Paul Scuffham

The authors assess the performance of availability utility-based instruments for people with dementia by comparing their psychometric properties and explore factors that cause variations in the reported health values generated from those instruments by conducting meta-regression analyses.

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Health Technology Assessment for Medical Devices Continues to Be a Struggle

By Christiane Truelove

In healthcare technology assessment (HTA) for medical devices, the problems worldwide remain in considering how a device or diagnostic has healthcare value, determining which standards should be used in the assessment, and using those standards to develop proper assessment tools. The United States, in particular, has a fragmented assessment landscape with a host of payer, provider, and independent assessment groups creating their own standards and manufacturers opting to work with the ones that work the best for them. Although European countries each have a single HTA body and the European Union (EU) in 2017 implemented new regulations for medical devices, experts attest that on the ground in certain countries, there still does not exist a comprehensive approach to systematically assess medical devices and diagnostics. However, there is a new proposal in the EU to reinforce cooperation between member states when it comes to HTA. Meanwhile, ISPOR has been working to highlight the value frameworks issues specific to individual technologies, and this is a conversation that will continue for some time to come.

> "You don't have people writing letters to *The New York Times* and the *Wall Street Journal* about the high price of medical devices."

FINDING THE EVIDENCE: WHAT IS VALUE?

As Eric Faulkner, vice president of Precision and Transformative Technology Solutions at Evidera, points out, most of the techniques of evidence-based medicines were developed around drugs, not devices or diagnostics. "Therapeutic medical devices often have this challenge of being integrated into a procedure, whether that's a surgical procedure or some other procedure. They're different than drugs because they're not always eligible for separate payments," Faulkner says. "And that influences what kind of evidence can be developed."

Devices are also different from drugs in that there are different levels of risk classifications and applications—for an example, an artificial heart versus a drug-eluting stent versus a tongue depressor. "There are over 100,000 types of medical devices that fall into buckets," Faulkner says. "So ISPOR has been working to think about how we characterize value frameworks for different types of device applications."

Drugs have been under a much greater pricing scrutiny over the past few years. "Devices have not been on the radar screen to the same extent," Faulkner says. "You don't have people writing letters to *The New York Times* and the *Wall Street Journal* about the high price of medical devices." This also means some of the policy changes about pricing will be less focused on device issues, because on some level there is a bundled payment system.

But this opacity in pricing also creates the challenge of defining what is "value based" reimbursement and payment when considering devices and diagnostics. "It's easy to get there for drugs, because except for in-patient scenarios, they are discretely reimbursable," Faulkner says. "They're not bundled into a procedural payment or an episodic care payment."

In determining outcomes versus cost for medical devices, it is a struggle for device manufacturers to provide the type of evidence that payers and health technology assessors prefer because most medical devices do not undergo randomized clinical trials, as manufacturers are able to use the evidence generated by other devices in the same class. Because the pivotal studies for devices are very different in design, this creates challenges on the payer side, as payers are seeing different types of evidence and there is a lot more variability with how that evidence can be assembled.

On the diagnostics side, Faulkner says, "it's even more challenging because the rules of the road for diagnostics in terms of what a "good" study looks like have been a moving target for the past 20 years. We're starting to see some global movement with groups such as INAHTA (International Network of Agencies for Health Technology Assessment), where there have been multiple steps to define what "good" looks like for diagnostics, but we really haven't landed on something that's consistent and homogenous. And to a certain extent that's also true for devices."

At the same time, there are no homogenous standards for evaluating medical devices, even those within the same class. "The device industry and associations have been working a long time on something that's a little more predictable and even better aligned to some of the unique attributes of devices, but the challenge is that the HTA agencies and payers basically have to deal with what is in front," Faulkner says. "So they may not have as much time to step back and create from scratch a picture of what the data should look like from an evidentiary perspective, including outlining all of the nuances of different types of device applications, taking into account things such as level of invasiveness to the patient, classification, and many other features."

It may be up to device manufacturers to come up with the standards of what "good" evidence looks like, Faulkner says. "And until that happens more comprehensively, the same dialog we're continuing to have today may recycle for many years."

IN THE US, A FRAGMENTED HTA LANDSCAPE

Medical device manufacturers in the United States have to deal with 3 different payer groups: the government (through Medicare and Medicaid, the Department of Defense, and the Veterans' Administration); private insurers; and employer-sponsored health plans. "Depending on who is paying for this equipment, covering the cost of the medical devices, and what sorts of contractual arrangements exist, costs may be bundled into a service or procedure, but can also be standalone, defined contract reimbursement for those particular devices," says Dominic Galante, chief medical officer of Precision for Value.

An example of a bundled payment scheme for medical devices are hip or knee replacements. The in-patient cost involves a DRG (diagnostic-related group) reimbursement. This means the implant itself, no matter who manufactures it, is part of the DRG and is >

negotiated in contract with the payer, Galante says. The DRG payment also includes the surgery and supportive care.

A continuous glucose monitor or an insulin pump would not be part of a bundled payment, but would be considered a standalone medical device. However, their prices are also contracted and pre-negotiated under a durable medical equipment benefit and would be reimbursed at those rates. Bundled payments may make it more difficult to persuade payers to increase what is paid for a device, but renegotiations for add-on fees for contracts can still take place, Galente says.

For instance, if a manufacturer introduces a new pacemaker or neurostimulator and determines through HTAs and clinical reviews that there is significant evidence-based clinical outcomes and cost data, there is an opportunity to renegotiate contracts. "Add-on fees quite oftentimes are discussed and negotiated as part of contract enhancements by health systems, hospitals, or Medicare delivery systems for these types of circumstances," Galante says. "It doesn't always work out. There is a lot of variability and a lot of negotiations. The strength of the evidence is what drives most of those final decisions."

On the positive side, Faulkner believes that the 21st Century Cures Act will have a "profound" potential impact on spurring discussions on *value* for medical devices, as the legislation calls for the use of real-world evidence alongside clinical data in the US. "That gives devices and diagnostics some latitude to better define what kind of study or data collection method makes the most sense to characterize and address the risk-benefit requirements to the US Food and Drug Administration, and that also helps pull through to making a case for payers. Just like we saw with the evolution of patient reported outcomes from a 'nice to know' to a 'got to have,'" Faulkner says.

According to Faulkner, medical devices and diagnostics, as opposed to other technologies, may stand to benefit from the push for real-world evidence as "there is a lack of clarity about evidentiary requirements, at least from the payers' perspective. So some of that evidence not only can check a box for regulators, but can also help clarify issues that payers, physicians, or health systems are interested in."

The advent over the past few years of accountable care models "opens the door for devices to handle more comprehensive value demonstration and value discussion with providers," Faulkner says. "If they're able to come to market with data that show what the implications of the device are for the provider, taking into account incentives systems such as accountable care, then they may have the opportunity for a new type of dialog at the provider level. "

At this point, the United States does not have a systematic means in which HTAs are conducted, Galente says. "There are about 63 different HTA organizations just in the United States," he says. "There are government-based organizations, such as the Institute for Healthcare Research and Quality; there's the Institute for Clinical and Economic Review among the not-for-profit independent organizations; there are a host of private organizations, like the Blues technology organization, (which provides assessments for Blue Cross/Blue Shield health plans) Hayes Inc (which many payers contract with). "Without standardization and without a single entity to provide these reviews, payers will rely on whichever organization that they deem to be appropriate for them," Galante says.

NEW EUROPEAN REGULATIONS REQUIRE MORE A MORE UNIFIED APPROACH TO HTA

Faulkner notes that in Europe, as in the United States, medical devices are often embedded into procedures and are often not discretely reimbursable. Unlike the United States, however, each European country has its own HTA body—such as the National Institute for Health and Care Excellence in the United Kingdom—plus there are international initiatives such as the EUnetHTA Core Model.

However, even with these tools, there was no real unity in HTAs for medical devices. According to Sabine Fuchs, et al, the authors of "Health Technology Assessment of Medical Devices in Europe: Processes, Practices, and Methods," which was published in the January 2016 issue of the *International Journal of Technology Assessment in Health Care*, the existing tools were not broadly implemented.

"Despite growing consensus on their importance and international initiatives, such as the EUnetHTA Core Model, specific tools for the assessment of medical devices are rarely developed and implemented at the national level. Separate additional signposts incorporated in existing general methods guides may be sufficient for the evaluation of medical devices," the authors say.

> ...before new high-risk medical devices are approved, manufacturers will need to demonstrate clinical benefit, "defined as a positive impact on health that should be measured using patient-relevant clinical outcomes."

But there are going to be broad-ranging changes to HTA in Europe over the next 3 years, at least when it comes to medical devices. In April 2017, the EU published the new European Medical Devices Regulation and the In Vitro Devices Regulation to tighten how these devices are marketed in Europe. The regulations entered in force in May, giving medical device manufacturers a three-year transition period. According to EU officials, the regulations introduce better protection of public health and patient safety through stricter pre-market control of high-risk medical devices; a comprehensive EU database on medical devices (EUDAMED) that will contain a living picture of the lifecycle of all products available on the EU market; a new device identification system based on a unique device identifier that will allow easier traceability of medical devices; an 'implant card' for patients containing information about implanted medical devices that will make information easily available and accessible to the particular patient; and a robust financial mechanism to ensure patients are compensated in case they receive defective products.

Olberg and colleagues looked at what is going in Germany in "Evidence-Based Decision-Making for Diagnostic and Therapeutic Methods: The Changing Landscape of Assessment Approaches in Germany," which appeared in the October 2017 issue of *Health Research Policy and Systems.*

According to the authors, the changes to the European medical device regulations stimulated activities at the national level, as for example in Germany. "This becomes evident when considering legislative changes over past years that comprise a more tightened decision-making framework on hospital-based diagnostic and therapeutic methods … employing high-risk medical devices, making the use of HTA an essential aspect in the decision-making process," the authors say. "However, besides the increased activity of HTA in Europe and worldwide and the common remits, roles, and aims national healthcare systems share, there are differences in terms of its implementation and impact."

One of the therapeutic areas that will see more immediate impact from the new regulations and increased HTA activity is cardiology, which uses high-risk medical devices such as defibrillators and heart valves. As Piotr Szyma´nski, et al noted in "The New European Regulatory Framework for Medical Devices: Opportunities for Engagement by Electrophysiologists," published in December 2017 in *EP Europace*, "The previous European system of approval gave patients in Europe earlier access to new high-risk devices, compared with patients in the United States, but with a higher risk of complications."

The authors note that before new high-risk medical devices are approved, manufacturers will need to demonstrate clinical benefit, "defined as a positive impact on health that should be measured using patient-relevant clinical outcomes."

And in January 2018, the European Commission proposed to reinforce cooperation on HTA among member states. The proposed Regulation on Health Technology Assessment covers new medicines and certain new medical devices, providing the basis for permanent and sustainable cooperation at the EU level for joint clinical assessments in these areas. Member states will be able to use common HTA tools, methodologies, and procedures across the EU. The 4 main areas addressed are (1) joint clinical assessments focusing on the most innovative health technologies with the most potential impact for patients; (2) joint scientific consultations in which developers can seek advice from HTA authorities; (3) identifying emerging health technologies to determine early what are the most promising technologies; and (4) continuing voluntary cooperation in other areas. Individual EU countries will continue to be responsible for assessing non-clinical (eg, economic, social, ethical) aspects of health technology and making decisions on pricing and reimbursement.

"Cooperating on HTA on a sustainable basis at EU level should ensure that all EU countries can benefit from the efficiency gains, maximizing EU-added value," the European Commission stated in a press release. "Strengthened EU-cooperation in this area is widely supported by stakeholders interested in patients' timely access to innovation. Stakeholders and citizens who responded to the Commission's public consultation showed overwhelming support, with almost all (98%) acknowledging the usefulness of HTA and 87% agreeing that EU cooperation on HTA should continue beyond 2020."

Additional information:

For more information on the ISPOR Medical Device and Diagnostics Special Interest Group, go to https::/ispor.org/sigs/MedDeviceDiagnostics.aspx

By the Numbers

Section Editor: The ISPOR Student Network*

MILESTONES IN INNOVATION[1]

1815
René Laënnec invented the stethoscope

1895
Wilhelm Conrad Röntgen discovered the X-ray

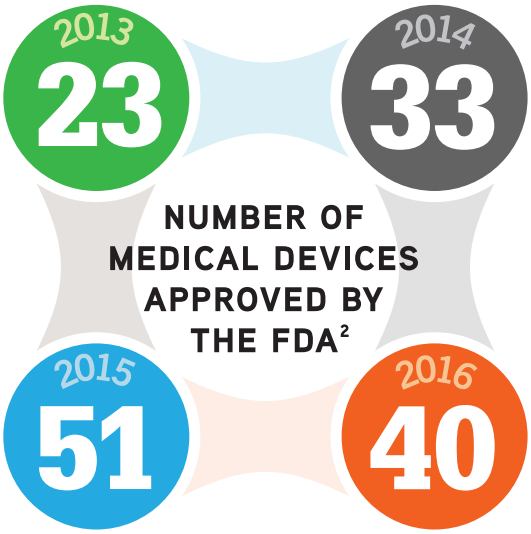
1943
Willem J. Kolff built the first dialysis machine

1958
Seymour Furman invented the pacemaker

1982
Robert Jarvick performed first artificial heart transplant

2013
Researchers from Cornell University printed an outer ear that works like and resembles the real thing

2016
Medtronic's MiniMed 670G, the world's first artificial pancreas, was approved by the FDA



MARKET SIZE

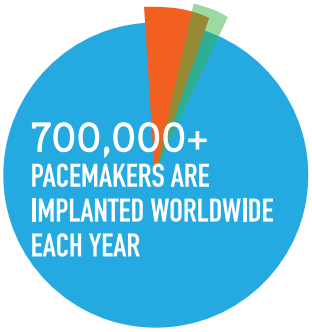
Estimated size of **MEDICAL DEVICES** market by 2022[3]

$26.75 billion

Estimated size of **IN-VITRO DIAGNOSTICS** market by 2021[4]

$96.93 billion

PREVALENCE



8% TO 10% OF THE US POPULATION[5]

AND

5% TO 6% OF PEOPLE IN INDUSTRIALIZED COUNTRIES HAVE AN **IMPLANTABLE MEDICAL DEVICE**[6]

Contributors: Jayesh Patel, Pragya Rai, West Virginia University; Kangho Suh, Blythe Adamson, University of Washington

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How Market Access Works for Medical Devices Is Different from Pharmaceuticals

Katarzyna Kolasa PhD, Kozminski University, Warsaw, Poland and Straub Medical, Wangs, Switzerland

KEY POINTS

Market access for medical devices requires a special approach, which should be different from the one for pharmaceuticals.

The role of real-world data for the value assessment of medical devices is growing.

There are different pricing and reimbursement pathways for medical devices.

DOES ANYONE REALIZE THAT THE MARKET ACCESS PROFESSION IS ACTUALLY SPECIFIC TO THE MEDICAL INDUSTRY?

There is an infinite list of different professions that can be easily tailored to different business environments but it does not apply to the role of market access. There is a simple explanation why we are so special in that respect. The healthcare sector differs simply from other commercial goods markets. It was already recognized in 1963 when Kenneth Arrow, in his distinguished article, "Uncertainty and the Welfare Economics of Medical Care," revealed a number of specific characteristics that make healthcare technologies so different from other commodities [1]. In contrast to the free market economy, there is no free exchange of goods in the healthcare sector. The demand for medical services is unpredictable and controlled. There is a need to engage a third party (physician) in the purchase-making decision. In addition to this, the entrance to the healthcare sector is extensively regulated and safeguarded by the number of institutions responsible for product registration as well as pricing and reimbursement (P&R). With all these hurdles, the market access function became extremely vital for any company operating in the medical industry.

It must be noted, however, that there is some variety in the complexity of entry barriers for different types of healthcare technologies (ie, pharmaceuticals and medical devices). Historically, the former group faced the most stringent P&R regulations, which, in turn, led to the development of different variations of market access expertise, such as health technology assessment (HTA), real-world data (RWD), public affairs, and value demonstration. The latter group, on the other hand, encountered fewer challenges with respect to market entry from a P&R standpoint [2,3]. Hence, one can make the claim that the market access area of expertise in the field of medical devices did not develop to the same extent, as is the case for pharmaceuticals.

New regulatory requirements, such as the European Medical Device Regulation 93/42/EEC and the growing number of HTA initiatives beg the question whether the future market access function in the field of medical devices might bear more resemblance to that developed for pharmaceuticals [4,5]. There is no doubt that the market access skillset (such as health economics, pricing, and HTA) required is equivalent, irrespective of the health technology. However, there are still a number of distinctive features within the medical device sector, which indicate the need for a different market access approach.

First, it has to be acknowledged that the P&R system regarding medical devices is more complex compared to that of pharmaceuticals. In the majority of cases, the costs of medical devices and associated medical procedures are covered by a diagnosis-related group (DRG)-based payment or other financing models based on resources consumed. In contrast to the reimbursement list of pharmaceuticals, the updates of DRG lists do not happen that frequently. In the United Kingdom, for example, healthcare resource groups (HRGs) are set up for two-year periods. In 2015, in total, there were more than 25,000 HRG codes, but only a handful of new tariffs were added [6]. The complexity of the P&R processes for medical devices also relates to the fact that there may be multiple reimbursement pathways. For instance, at least three different options exist for the market entry in France [7]. In addition to the DRG-based payment mechanism, there is a list of products and services qualifying for reimbursement. Some innovative medical devices may be introduced to the market by the decree of the Ministry of Health, as was the case for the drug-coated balloons used for treatment of arterial occlusive disease in the lower limbs [8].

Secondly, the complexities of market access in the field of medical devices stem from numerous factors that influence the performance of medical devices [2,3,9]. The correlation between technical success and treatment outcome depends not only on the medical device itself, but also on the patient's characteristics and history of the disease as well as the healthcare professional's experience with the medical device and overall healthcare system efficiency. It is not uncommon that various courses of action are available for any given health problem >

and that multiple procedures are initiated simultaneously. As such, the search for appropriate comparator devices and subsequently, the incremental value may be challenging to determine.

Lastly, the distinctive feature of market access challenges for medical devices stems from the lack of data. Until recently, the regulatory requirements have been much more limited for medical devices' manufacturers compared to those of the pharmaceutical industry. In the United States, clinical data are compulsory only for class III medical devices, while in the European Union, clinical data are required for Class IIa, IIb, and III medical devices, but typically are used only for the assessment of "conformity" [10]. In addition to the regulatory regulations, the lack of data stems from the fact that product development programs differ considerably between medical devices and pharmaceuticals. While the average time to market for a new pharmaceutical product averages about 12 years, the corresponding number for a medical device is just 18 months [11]. The lack of clinical data for medical devices can be exemplified by a recent systematic literature review. It was found that among 215 clinical trials conducted for 32 innovative medical devices, only 15% of them were randomized controlled trials and more than 50% included fewer than 30 patients [12].

The need for a different market access approach regarding medical devices does not stem entirely from the extraordinary challenges, which are not present while working with P&R requirements of pharmaceuticals. There are also a number of opportunities for the development of market access in the field of medical devices; at least two are worth mentioning.

Firstly, real-world data (RWD) are playing a bigger role in the decision-making processes regarding medical devices. In August 2017, the FDA issued guidelines on the use of RWE to support regulatory decision making for medical devices. As it was rightly stated, the "traditional" clinical trial may be impractical or excessively challenging to conduct. There were a number of reasons provided as to why RWD should be considered as a valid source of evidence. It was found that RWD could help to find historical controls or assist with hypotheses testing in a prospective clinical study. Following that important milestone taken by the FDA, CADTH started the discussion about RWD to generate evidence for HTA and reimbursement as well [13]. In some instances, RWD can be generated more easily than RCT in the field of medical devices.

As pointed out by E. Neugebauer and colleagues, the key issues with RCTs for medical devices are the difficulties experienced when accounting for blinding, defining the right comparator and adjusting for the learning curve of physician as well as determining appropriate outcomes and study outcomes [14]. At the same time, RWD may be much more accessible. Given that medical devices are typically utilized for some specific medical procedures that must be registered in the financial system anyway, the data regarding effectiveness and resource consumption may be available. Hence, the RWD could be more easily accessed and less time-consuming to acquire compared to RCTs. Although the clinical efficacy and direct comparative data would remain as a challenge, RWD effectiveness data are much more valuable from the payer standpoint.

Secondly, it should be noted that market access approach should take into consideration not only national P&R challenges but local restrictions as well. In that respect, some new trends at the local level, such as value-based procurement, are worth mentioning. The tender process is a very common gateway to the reimbursement system for medical devices in many countries. Following a new EU legislature with respect to public procurement, there is a requirement to introduce a new set of non-price–related criteria while purchasing [15]. The EU directive explicitly calls out the price-to-quality ratio as a driver to the decision-making process. If one connects that major legislature change with new methodological developments for health economics, such as multi-criteria decision making (MCDA), it will result in market access opportunities with respect to the evidence-driven, value-based framework at the local decision-making level.

In conclusion, market access for medical devices is a different "war game." There are various distinctive features of the medical device market, such as the importance of the relationship between treatment outcome and patient's characteristics as well as physician's experience, unavailability of RCTs, and complexity of P&R decision making. As a result, one should take a different perspective on market access's challenges and opportunities. Still there is definitely room for the introduction of the HTA in similar fashion as was the case for pharmaceuticals. Given how much budget is spent on medical devices and the corresponding medical procedures, there is a real need for optimal resource allocation with respect to financing. Hopefully a very pragmatic approach to outline the key distinctive features presented above will help in the debate regarding how the market access process should be shaped in the future for medical devices. Continued effort from ISPOR is necessary to further develop methodological guidelines regarding the role of RWD, HTA, and MCDA in the field of the medical devices and is especially welcomed.

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Potential Utility of Idiographic Clinical Trials in Drug Development

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KEY POINTS

Idiographic clinical trials offer a rigorous alternative to randomized controlled trials when the latter are not feasible due to available sample size, funding, or early phase in clinical testing.

Idiographic clinical trials combine subject-as-own-control designs with hierarchical linear modeling that has been tailored specifically for small sample-intensive, within-person analysis.

Idiographic clinical trials are flexible, have been used for a breadth of settings and clinical outcomes, and can be used to address complex treatment questions including safety, drug dosage, and comparative efficacy.

An innovative methodology — idiographic clinical trials (ICTs) — is introduced as a way to inform randomized controlled trials (RCTs) in terms of RCT planning (eg, sample size, effect size), use in research scenarios when RCTs are not feasible (eg, rare diseases with small populations), or use in applied settings such as clinical practice, where RCT parameters cannot be followed. ICTs can be conducted generally for lower cost with faster completion time than RCTs. ICTs should not be seen as replacements for RCTs, but as a way to help inform RCTs or provide insights for early product development without allocating the resources for an RCT for early evaluation of an asset. The term idiographic clinical trials comes from its emphasis on within-individual processes over time. Compared to RCTs, this approach is adept for early phase clinical trials, pilot studies, and testing whether efficacy from an RCT can be replicated in a specific clinical setting or subpopulation (eg, patients with RCT exclusion criteria). ICTs couple two well-known methodologies to yield rigorous results from small samples: subject-as-own-control experimental designs (eg, crossover designs) with hierarchical linear modeling (or multi-level modeling) refined specifically for small samples.

> ICTs couple two well-known methodologies to yield rigorous results from small samples: subject-as-own-control experimental designs (e.g., crossover designs) with hierarchical linear modeling (or multi-level modeling) refined specifically for small samples.

RCTs

RCTs represent the "gold standard" for evaluating efficacy and safety of pharmaceuticals and biologics for regulatory purposes. RCT key features include randomization, blinding, comparison group(s), and isolation of key findings to treatment conditions, all of which contribute to RCTs' high internal validity. RCTs frequently assess an intervention's effect against alternative interventions or no intervention, while minimizing numerous types of bias. Conversely, RCT disadvantages include use of exclusion criteria (limiting their generalizability); unbalanced attrition (ie, patients in one arm are more likely to drop out, as when those in a usual care arm get sicker sooner and drop out); ethics (eg, it is unethical to give some patients placebo); and investigator discretion (eg, decisions about cross-over may be left to physicians/investigators potentially violating randomization), all of which can reduce an RCT's external validity. Moreover, RCTs typically require large budgets, recruiting hundreds to thousands of participants, and up to 18-month follow-ups per participant.

Hence, RCTs are often a balance between costs, time commitments, internal/external validity, choosing a comparator or no head-to-head comparison, and so on.

In early phase trials when establishing a new compound's efficacy, safety, and potential dosing, an RCT may be too expensive or time-consuming or not even feasible (eg, for rare diseases). If the signal-to-noise ratio indicates treatment is not efficacious, a company could lose millions of dollars. A faster and less-expensive option to an RCT could clearly benefit companies exploring new assets. Rigorous ICTs require rarely more than 50 participants, less than 3 months' duration per participant, can address multiple early trial questions in one sample (safety, efficacy, dosage, differences among subgroups), and offer individuals personalized efficacy (termed "impact"), which is a strong incentive to participate and not attrite, all of which may reduce costs. However, ICTs do have should be some limits and may be only used under under specific circumstances. >

A COMPLEMENTARY ALTERNATIVE

Subject-as-own-control experimental designs (eg, crossover and staggered baseline designs) provide the data collection structure for ICTs. Time series data are collected from each participant during a control (or care as usual) time period/phase and experimental treatment(s) time period/phase(s). Many potential confounds are managed because the same participants provide control and experimental data (rather than randomization). To illustrate, random blood glucose test in patients with type 1 diabetes might be observed repeatedly while receiving standard treatment (control phase) and then again during an experimental treatment (treatment phase) [6]. By randomizing length of control phases among participants and varying their study enrollment dates, potentially confounding factors of practice effects, disease natural history, human development, and historical events are controlled. If efficacy estimates are desired from an ICT, participants ought to resemble the population heterogeneity. By coupling subject-as-own-control designs with statistical techniques such as hierarchical linear modeling that is tailored specifically for intensive within-person analysis, they provide highly flexible, rigorous clinical trials. The analytic techniques account for well-known sources of bias including autocorrelation and limitations of visual inspection [1-4]. Introductory papers to ICTs provide more technical details using study illustrations [5-10].

Several strengths of ICTs stem from their far smaller samples, shorter durations, and resultant less cost and time compared to RCTs. If an asset shows a strong enough effect, a company could then use a traditional RCT. If the asset effect is not strong, a decision to not pursue that asset means much less cost and time invested compared to using an RCT to reach the same decision. ICTs can often be used when RCTs are not feasible. ICTs can be used frequently in clinical settings where strict adherence to an RCT protocol may not be possible (eg, ICU patients receiving critical care or when every participant requires the treatment), take advantage of natural experiments, or using quasi-experiments that occur during usual clinical care. Two recent examples were comparative studies between medications for emergency care sedation [5,11] and immunosuppression for recipients of liver or kidney transplants [12].

ICT LIMITATIONS

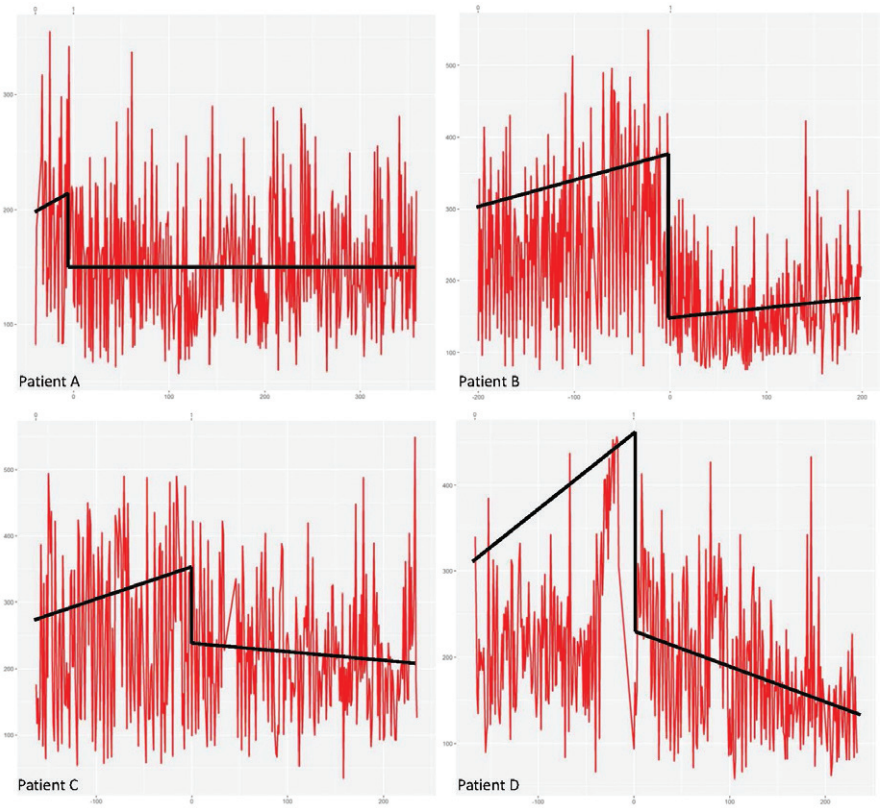
ICTs typically do not provide efficacy for large populations (intensive within-person protocols preclude large samples). Rather, their strengths and limitations provide complementary, patient-centered evidence, much of which can inform subsequent RCTs. ICTs can raise the rigor of early phase trials, orphan drug testing, effectiveness replications of efficacy estimates, and comparative outcomes research involving rare diseases. In addition, ICTs offer limited utility for short-lasting illnesses (common cold, influenza). To illustrate, repeated measurements are usually not feasible during the period of myocardial infarction thus precluding ICTs, whereas ICTs may be ideal for a novel treatment for recovery from myocardial infarction. The following illustrations demonstrate some ICT uses, ranges in complexity, data types, and treatment development stages.

ILLUSTRATION 1: PILOT STUDY OF EFFICACY AND SAFETY

While developing and testing a treatment, ICTs could inform resource allocation, human effort, and time. Erroneous Go/No Go decisions risk (a) costly investments in compounds that end up being unsuccessful or (b) missing lucrative opportunities to develop efficacious medications [13]. ICTs could inform decisions about whether to pursue subsequent clinical phases and provide estimates of effect sizes and patient variability to design them. Illustration 1 demonstrated a pilot ICT that yielded evidence regarding efficacy, within- and between-person variability, and safety. Its small sample illustrates ICTs' potential uses for pilot studies and orphan drug testing.

Diabetic blood glucose is managed in nursing homes by using the sliding scale, which consists of adjusting insulin doses biweekly. Because of large spikes and drops in glucose that occur daily, sliding-scale glucose management often leads to ketoacidosis, unconsciousness, and organ

Figure 1: Manual Pancreas ICT Results Visualized at N=1 Level



Note: X-axis is sequential observations at meals or snack times (4 per day). Y-axis is blood glucose level (mg/dL). The Care-as-Usual phase spans observations prior to "0" (on x-axis); Manual Pancreas was administered thereafter (phases also are indicated by "0" and "1" above each plot).

damage. Contemporary glucose treatments are not used because of cost, potential damage to equipment (eg, glucometers), and a lack of incentives to change. A recently devised algorithm determines bolus insulin dosage based on a patient's blood sugar level and food intake during a meal [6]. Termed "manual pancreas," nurses draw blood to determine glucose levels, enter nutritional values of an anticipated meal, and administer bolus insulin based on the algorithm output. The nursing home where manual pancreas was pilot-tested admitted four patients during the study period.

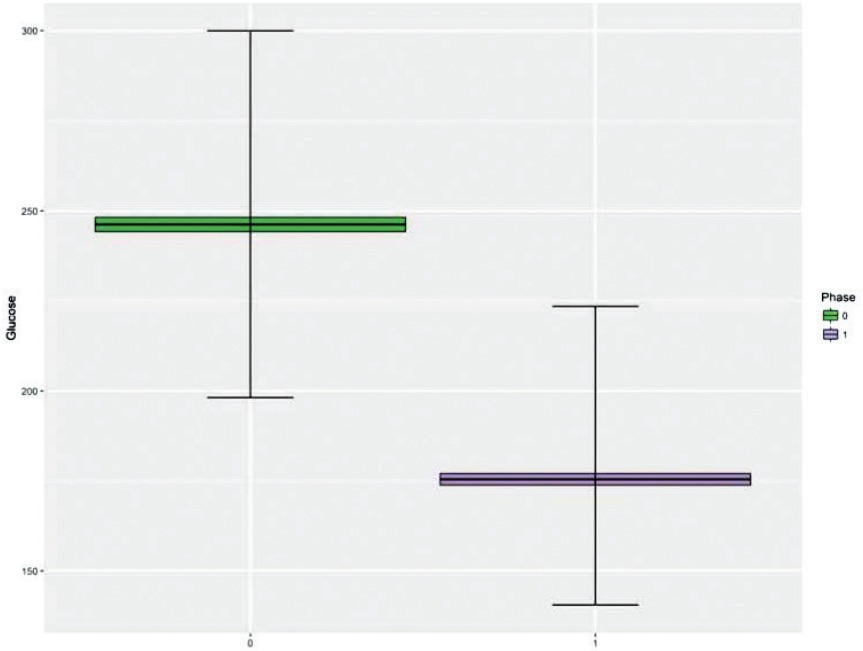
Figure 1 presents participants' modelled trajectories superimposed on observed glucose levels 4 times per day over 100 days. Each participant experienced an instant drop in blood glucose when manual pancreas was initiated, albeit to varying degrees. Variance in blood glucose illustrates how within-person patterns may interfere with interpretation of results and the importance of parsing out autocorrelation to obtain unbiased estimates. Relevant to this study is the circadian rhythm of blood sugar levels, which varies in periodicity among individuals. To test for interactions between manual pancreas and circadian rhythms, analyses were re-conducted separately for each time of day (Table 1). At certain meals, manual pancreas was associated with no improvement. Hence, to avoid safety risks associated with injections, manual pancreas could be skipped for patient A at breakfast and lunch whereas for patient C, manual pancreas could be limited to lunch.

Table 1: Change in Blood Glucose with Manual Pancreas per Time of Day

	Breakfast 7:30am	Lunch 11:30am	Dinner 4:30pm	Snack 8:30pm
Entire Sample	-35.9 (9.8)	-43.3* (194.2)	-59.4 (9.7)	-59.1* (277.9)
Patient A	0.2* (11.1)	1.8* (24.4)	-50.4 (20.2)	-104.2 (19.4)
Patient B	-32.2 (8.8)	-117.3 (23.0)	-156.3 (19.3)	-122.2 (17.0)
Patient C	11.5* (27.5)	-66.6 (26.8)	-35.5* (25.4)	3.0* (27.7)
Patient D	-112.1 (16.0)	26.3* (17.6)	43.5 (17.7)	-57.3 (24.3)

*Note: *Change in glucose was NS (P>.01). Parenthetical values are standard errors.*

Figure 2: Manual Pancreas ICT Aggregate



Note: Center of boxes represent mean blood glucose levels (mg/dL), 95% confidence intervals appear as upper and lower levels of boxes, and whiskers depict the standard deviations.

Figure 2 illustrates how an ICT can inform a subsequent RCT. The box-and-whiskers summary presents care-as-usual versus manual pancreas in terms of mean glucose levels, 95% confidence intervals (tops and bottoms of boxes), and standard deviations (whiskers). Inasmuch as the ICT sample resembles the clinical population of interest, results provide unbiased estimates for RCT planning.

Regarding safety testing, two patients were admitted to an emergency department during care-as-usual phases due to complications from ketoacidosis. During manual pancreas phases, no patient required emergency care. Moreover, clinical staff observed one patient to be far more alert and responsive during manual pancreas, presumably due to lower blood glucose. No health risks were observed related to the manual pancreas; however, repeated use of injections merited caution.

Also illustrated is ICT's provision of person-centered data. Recent movements such as precision medicine and evolving methodologies such as genetic micro trials provide opportunities for ICTs. These methods also can be used for testing mechanisms of outcomes while a treatment is being administered. Far more sophisticated analytics (eg, state-space modeling) are available for testing multivariate processes and outcomes [14].

ILLUSTRATION 2: DIFFERENTIAL/ COMPARATIVE EFFICACY

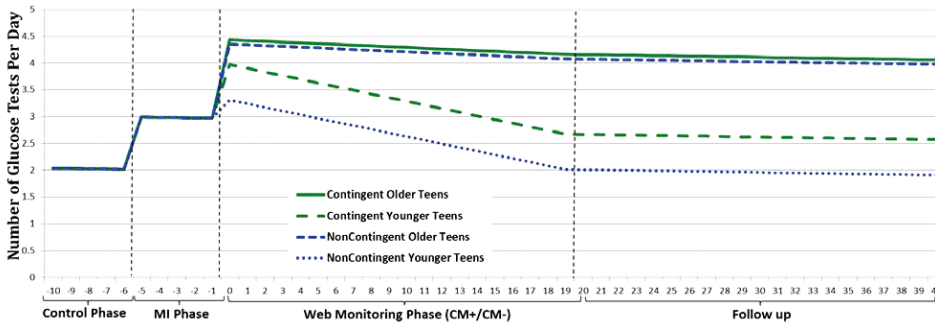
Comparative efficacy encompasses how outcomes differ between treatments or among subpopulations in response to a treatment. For example, if a large clinical trial demonstrates null or small efficacy, homogeneous subgroups may nevertheless respond well to the treatment. A subgroup also may respond poorly to a medication, thereby reducing the apparent overall efficacy. Traditional RCTs are frequently not designed to detail subgroup differences, >

especially if subgroups are not identified a priori. If during an RCT, insight is gained regarding a subgroup that responds differentially to a medication, an ICT could test the hypothesis. Illustration 2 presents results from a behavioral intervention to demonstrate ICTs' potential utility to address differential efficacy.

Over 200,000 US citizens with diabetes are younger than 20, most of whom have type 1 diabetes (T1D) [15]. Adolescent management of blood glucose is especially important, given diabetes' chronicity and cumulative health problems. However, as diabetes management shifts from parent to adolescent, glycemic control usually declines and is poor on average in adolescents [16]. A fundamental step in T1D management is taking four or more glucose tests daily; each additional daily blood glucose test is associated with 0.4% decreased glycated hemoglobin (A1C) [17] and in turn 10.5% decreased risk of diabetes-related complications [18,19].

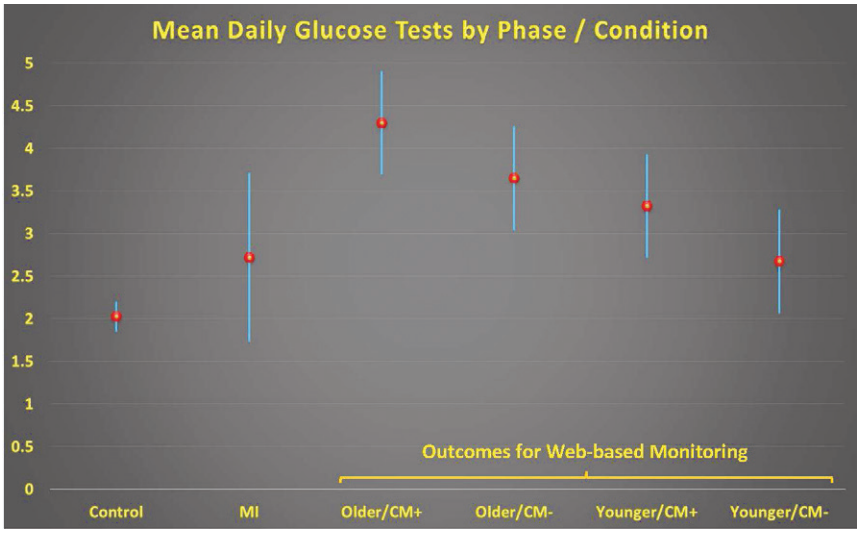
A program recently designed to increase daily blood glucose tests involved adolescents recording their glycemic tests over streaming video and entering test results at the study monitoring website (validated by glucometer readings) [20]. One study objective was to demonstrate the web program's clinical utility over and above two interventions with previously documented efficacy (motivational interviewing, or MI, and contingency management, or CM). In addition, its differential efficacy was compared between ages 13 to 15 versus 16 to 18.

Figure 3: Four-subgroup Trajectories of Tests Completed per Study Day



Note: The corresponding MMTA equation is Frequency of Daily Tests = 1.9885 - 0.00501 (per study day) + 0.9805 (for motivational interviewing) + 1.3240 (during treatment phase) - 0.06317 (per day of treatment phase) + 1.0430 (older teens during treatment phase) + 0.6598 (while receiving CS) - 0.05378 (per day of treatment phase for younger teens). Each model parameter reached P<.01 statistical significance.

Figure 4: Mean Daily Glucose Tests by Phase / Condition



A hybrid ICT-with-randomization design was used. Following a control phase with no intervention, MI was provided to all 41 participants to account for its effects. Next, participants received the web program with randomized CM+ (monetary rewards were contingent upon completing glucose tests; n=23) or CM- (the same monetary amounts were provided, but randomly; n=18). Gender and age group stratified CM randomization.

Figure 3 presents results as trajectories among four subgroups. During the control phase, all subgroups averaged two glucose tests conducted per day. Following MI, all subgroups increased about one glucose test per day and maintained this improvement. When the web monitoring program (plus either CM+ or CM-) began, differential efficacy occurred as an interaction between randomization and age group. Older adolescents and CM+ were associated with more daily glucose tests compared to the alternative subgroups. Younger participants gradually lost the benefit of web monitoring, whereas older participants largely maintained their benefit. After withdrawing all interventions, each subgroup's outcomes slightly decreased. Box-and-whiskers visualization of results more closely resembles traditional efficacy estimates (Figure 4) by depicting the signal-to-noise ratio similar to RCTs (e.g., for later phase clinical trials).

CONCLUSIONS

This introduction demonstrated how early phase ICTs might inform efficacy of an intervention at lower cost and faster than RCTs. When assessing whether a new asset has a sufficient effect and further development is justified, ICTs may be a more efficient and less-expensive alternative to RCTs. Software, methods for data collection, and analytics for multi-episode data are readily available, so these methods can be implemented now. As noted earlier, ICTs cannot replace RCTs. However, given the rigor of ICTs, the amount of data collected per patient, and the ability to learn the effect of alternative interventions/doses (i.e., treatment-/dose-switching becomes a time-varying covariate), ICTs can be a rich source of data for evaluating treatment effects as well as patient and disease progression.

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Additional information:

The preceding article is based on a workshop given at the ISPOR 19th Annual European Congress.
To view the authors' presentations, go to: https://www.ispor.org/Event/ReleasedPresentations/2016Vienna#workshop presentations

Stochastic Modeling in Health Economics and Outcomes Research: Common Mistakes and How to Avoid Them

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KEY POINTS

Three common mistakes are made in using stochastic modeling in health economics and outcomes research.

An intuitive explanation of why these are mistakes.

Appropriate techniques—and reference to further reading—on how to avoid the mistakes

STOCHASTIC MODELING IN HEALTH ECONOMICS AND OUTCOMES RESEARCH

Stochastic modeling is a commonly used methodology in health economics and outcomes research (HEOR) with two main purposes: (1) to assess and predict the level of confidence in a chosen course of action and (2) to estimate the value of collecting additional data to better inform the decision [1]. Because implementation of stochastic models can be difficult, we have identified several common mistakes through our stochastic modeling work in HEOR and elsewhere. These include:

(1) Confusing stochastic uncertainty and parameter uncertainty.
(2) Multiplication of probability distributions that represent stochastic uncertainty.
(3) Duplications of uncertainties and assuming independence.

Although these mistakes have been described individually, our objective is to raise attention to these mistakes in an intuitive way, describe the conceptual thinking behind the mistakes, and identify appropriate techniques to avoid them. We believe this provides a useful and complementary perspective for practitioners on how to avoid these mistakes and build correct stochastic models.

Following the ISPOR-SMDM Modeling Good Research Practices Task-Force, we distinguish two broad categories of models: (a) patient-level stochastic simulations that simulate events occurring at the individual patient level, (eg, state-transition microsimulations) [2] and discrete event simulation models [3]) and (b) cohort models that focus on groups of patients, and do not explicitly model differences between patients [1].

COMMON MISTAKE 1: CONFUSING STOCHASTIC UNCERTAINTY AND PARAMETER UNCERTAINTY

Stochastic modeling is often thought of as a method of quantifying and considering all uncertainty within a system. Here we will define parameter uncertainty in the context of statistical precision, (ie, the lack of knowledge about the true value of a model parameter or parameters). This is often called parameter uncertainty, uncertainty, or second-order uncertainty. In contrast, stochastic uncertainty refers to differences observed in a population due to chance or that can be assumed to be due to chance. This is also called variability, randomness, or first-order uncertainty. Following this idea, the confidence interval of a model parameter expresses parameter uncertainty, whereas a distribution of say, different treatment costs between patients, describes stochastic uncertainty ("variability").

> ...our objective is to raise attention to these mistakes in an intuitive way, describe the conceptual thinking behind the mistakes, and identify appropriate techniques to avoid them.

When applying stochastic modeling in HEOR, a common mistake is to focus on what at first sight may be the most important sources of uncertainty, and applying probability distributions to those. For example, based on a clinical trial of a healthcare technology, it may be apparent that for some patients there may be large beneficial effects while for others very little or none. If data are available, the analyst may then fit a probability distribution such as a lognormal distribution to individual patient benefit data and use it in a probabilistic model. The following are a few modified (example) sections of peer-reviewed papers that used cohort-based, state-transition models that illustrate the above thought process:

"The Monte Carlo simulations of the model were performed, using microsimulations trails with 1000 hypothetical patients"

"The costs of treatment per month were modeled using a lognormal distribution with a mean of $860 and a 95-percentile of $530-$10,000"

However, this approach is incorrect for the following main reasons:

1. **Stakeholder's societal perspective:** Probabilistic analyses are typically performed considering the societal perspective (eg, third party, governmental or insurance firm). This implies that decision makers are interested in the results for cohorts of target patients rather than in individual patient's variations (IPV). Thus, probabilistic analyses should be based in population-level statistics (typically the mean/expected value) and how the parameter uncertainty in these estimates affects the model conclusions. In other words, the probabilistic analysis should focus on the uncertainty in the expected results rather than the IPV results. This parameter uncertainty often will be close to normally distributed due to the central limit theorem, but if the target population is very small (ie, in the hundreds) and or/the IPV is very skewed, the parameter uncertainty of the expected CE might not be normal.

2. **Mixing stochastic uncertainty and parameter uncertainty and incorrect probability distributions:** Furthermore, the analyst may be mixing up different uncertainty concepts. A fundamental component of any stochastic analysis is a probability distribution, and many different probability distributions exist such as the Normal (Gaussian), Lognormal, Gamma, Binomial, and Beta distributions. For anyone performing a stochastic analysis, it is therefore important to use the correct probability distribution. Related to this, ISPOR guidelines [1] also emphasize the importance of precision regarding terminology. The connection between the ISPOR guidelines and including different "sources of uncertainty" within a stochastic model is summarized in Table 1.

Despite these guidelines, often the probability distributions included in probabilistic analyses represent not only parameter uncertainty, but also stochastic uncertainty (ie, randomness or inter-individual variability).

Table 1. Overview of how to include different sources of uncertainty in decision modeling (based on reference 1).

Uncertainty for decision modeling, preferred terms (1)	How modeled within a probabilistic analysis	Example probability distributions used	Comments
Stochastic uncertainty (also called first order uncertainty or randomness)	Variability (and inter-individual variability) distributions	Bernoulli, Binomial, Poisson, Lognormal, Gamma, PERT, and Triangular	Treats differences in the realization of individual, patient-level, outcomes as random variables. Should only be included in the 'inner loop' (i.e. the microsimulations) in individual patient-level models
Parameter uncertainty (also called second order uncertainty)	Uncertainty distributions, representing '"lack of knowledge' knowledge" about the parameters	Beta, Normal, Student, Gamma, Inverse Gamma, Dirichlet, and Wishart	Should be included in all probabilistic models
Heterogeneity	Structural, since this is variability that can be explained (therefore, this is not stochastic)	Not applicable	This is the variability that can be attributed to known characteristics of patients
Structural uncertainty ("model uncertainty")	Model ensemble or model averaging	Not applicable	Can be examined by using structurally different models

It is important to note that in patient-level stochastic models, stochastic uncertainty should be included to simulate events occurring at the individual level [1]. However, if the decision maker is not interested in understanding individual patient-level outcomes, the inclusion of stochastic uncertainty typically requires running two separate simulation loops to obtain the expected outcomes (5). The outer loop would only simulate the parameter uncertainty, while the inner loop (ie, the microsimulation) would simulate the stochastic uncertainty to get the expected outcomes.

In conclusion, to avoid this mistake, it is important to have a clear understanding of the difference between stochastic uncertainty and parameter uncertainty. In most cases, only include distributions that represent parameter uncertainty and not use distributions that represent stochastic uncertainty, unless (1) decision makers are interested in patient-level outcomes and (2) the stochastic uncertainty distributions are within an inner loop of a probabilistic model.

COMMON MISTAKE 2: MULTIPLICATION OF DISTRIBUTIONS THAT REPRESENT STOCHASTIC UNCERTAINTY

Starting in elementary school, we are all taught that multiplying 25 times 40 resulted in 1,000. Multiplications are often used as a shortcut for a sum of identical numbers. However, probabilistic models, by definition, include random numbers, so sums cannot be calculated typically via a product. Imagine that we're trying to estimate the annual costs of a certain treatment:

— Treatments are needed at a mean rate of 25 per year and are Poisson distributed.

— There is IPV around the cost per treatment, which is lognormally distributed with an average cost of $40 per treatment and a standard deviation of $30.

A common calculation is to multiply both distributions within a Monte Carlo simulation model, (ie, Annual cost = Poisson [rate = 25] x lognormal [mean = 40, standard deviation = 30]).

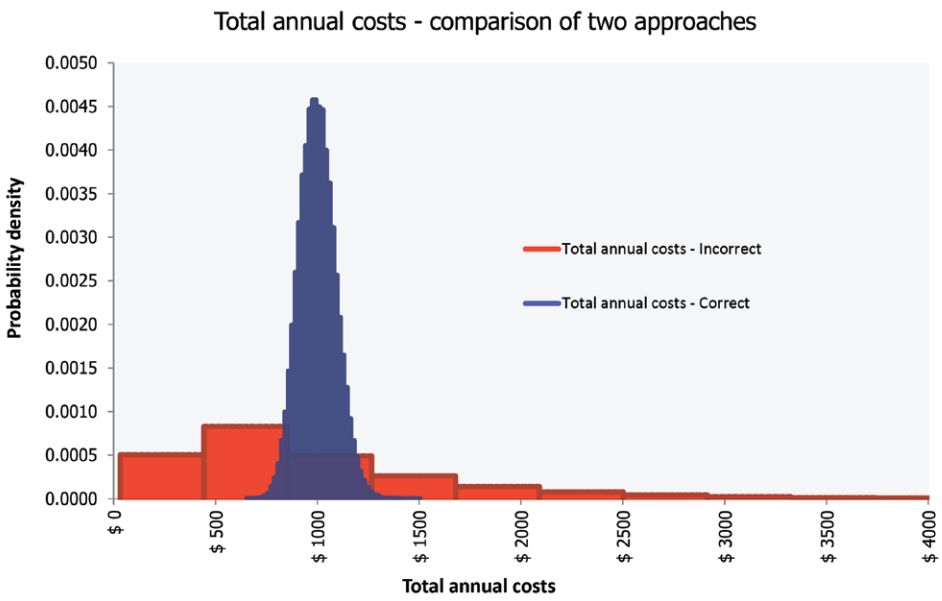
This product is incorrect because it assumes that all samples within an iteration are identical, (ie, the opposite of stochastic uncertainty). Let's walk through a few hypothetical model iterations (random samples) to understand this mistake. In iteration #1, the Poisson distribution (rate = 25) yields 30 treatments and the lognormal (mean = 40, standard deviation = 30) yields a cost of $100/treatment, resulting in total costs of $3,000. In iteration #2, the model samples 25 treatments with a cost of $30/treatment for total costs of $750. As you can see, by multiplying the distributions we are assuming that within one iteration, all treatments cost the same, whereas our lognormal distribution shows that some of these treatments will be cheap and >

some will be expensive. There are several approaches to sum distributions correctly, including:

1. Simulating individual treatments, events, or patients, which is intuitive as it would simulate a unique cost for each of the treatments. Some treatments will have high costs while others will have lower costs. For the example, Figure 1 shows the difference between the incorrect approach (gray) with the correct approach in situation 2 (black). As Figure 1 shows, the incorrect approach results in a considerable overestimation of the amount of uncertainty of total annual costs.

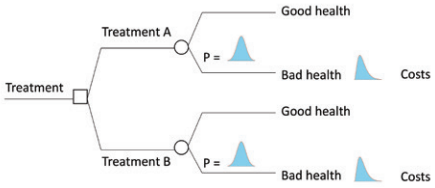
2. Aggregate or compound distributions: these allow for a single-pass version of the calculation above. The most common is the central limit theorem, which is a technique that has been described extensively, and provides a good approximation when n (in this case the number of treatments) is large (typically > 30 is used as a rule-of-thumb). However, this method doesn't work when the distributions modeled are correlated. Other methods such as the Fast Fourier Transfer and the Methods of Moments methods allow approximate calculations in certain specific situations and can incorporate correlations.

Figure 1. Comparison of total annual costs with incorrectly multiplying first-order uncertainty distributions and with correctly simulating costs of individual treatments



Note that distributions representing parameter uncertainty (as opposed to IPV as discussed here) can be multiplied because they represent a single but imperfectly known value.

Figure 2. Example cohort-level, state-transition model



COMMON MISTAKE #3: DUPLICATIONS OF UNCERTAINTIES AND ASSUMING INDEPENDENCE

Consider the simplified cohort-based state transition simulation model displayed in Figure 2. Epidemiological data suggest that "P" (probability of "bad health") is different between Treatment A and Treatment B. With regards to the expected costs of "bad health," the estimates are based on empirical data that are not specific to either treatment A or B. Based on the model described in Figure 2, the stochastic analysis may include four parameter-uncertainty distributions:

1. Parameter uncertainty for P (bad health, given treatment A),
2. Parameter uncertainty of P (bad health, given treatment B),
3. Parameter uncertainty of the mean costs of bad health if given treatment A, and
4. Parameter uncertainty of the mean costs of bad health if given treatment B.

In this case, the CE analysis correctly used two separate parameter-uncertainty distributions for each of the two probabilities of "bad health," given that empirical data suggested there is a difference between both treatment arms. However, for the distribution describing the expected costs of "bad health," no empirical data were available to estimate that this would be different between both treatment arms. Therefore, only one probability distribution should be included and not one for each treatment arm separately. In more general terms, in stochastic CE analysis it is common to assume that distributions are independent ("uncorrelated"). Because this is the default situation in most software packages, this is a common assumption, even though it may not be valid.

In the above state-transition model example, the correct way would be to include only one distribution of costs of "bad health," and use this distribution for both treatment arms. While counter-intuitive at first, correctly including only one distribution in this analysis would increase the total uncertainty around the results. With regards to the common mistake of assuming independence between distributions, a detailed discussion of this is provided by Briggs et al [1], with the advice that correlations among parameter uncertainty distributions should be considered. When data is avialble, joint uncertainties can be estimated using methods such as Bayesian Markov Chain Monte Carlo or bootstrapping.

CONCLUSION

Our hope is that by providing the conceptual thinking behind the above three common mistakes, this article provides a useful and complementary perspective to good practices on stochastic modeling, such as those described by the ISPOR-SMDM Modeling Good Research Practices

Task Force Working Groups [2]. For more detailed and technical insights, we encourage readers to review the referenced papers.

(Note: We have not included references to publications that make such mistakes, as the purpose of this article is to point out to those mistakes rather than providing a systematic review of publications with methodological errors).

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Additional information:

For more information on ISPOR's work with modeling, readers may go to the ISPOR-SMDM Modeling Good Research Practices Task-Force at https://www.ispor.org/workpaper/Model-Parameter-Estimation-and-Uncertainty-Analysis.asp.

Q&A

Real-World Evidence and Health Technology Assessment: An Interview with Lou Garrison, PhD

Our editorial board member for *Value & Outcomes Spotlight* was fortunate to catch up with Louis P. Garrison, PhD, Professor Emeritus, University of Washington, Seattle, WA, USA. Dr. Garrison served as ISPOR President for July 2016-June 2017, and currently serves as chair of the Past Presidents Council. He also recently co-chaired the ISPOR Special Task Force on US Value Frameworks, and is a member of the ISPOR Health Science Policy Council.

Dr. Garrison's research interests include national and international health policy issues related to pharmacogenomics and personalized medicine, regulatory benefit-risk analysis, universal insurance coverage, global differential pricing, value-based reimbursement and risk-sharing arrangements, as well as the economic evaluation of pharmaceuticals, diagnostics, devices, surgical procedures, and vaccines, particularly as related to organ transplantation, renal disease, influenza, measles, obesity, and cancer.

Value & Outcomes Spotlight: **It has now been more than 10 years since Peter J. Neumann, ScD and you co-chaired an ISPOR task force on real-world data (RWD). There seems to be growing emphasis on the use real-world evidence (RWE) in the context of health technology assessment (HTA). Can you explain the sudden resurgence?**

Lou Garrison: Our task force report was published in 2007, but our work began a couple of years before. So, ISPOR has been at this for well over 10 years, and has a lot of output and contributions from a number of task forces to show for it. As a scientific society, ISPOR has done a great deal to move this forward.

That first task force struggled with defining "real-world data" and with the distinction between RWD and RWE. In the end, we adopted an operational definition of "data used for decision-making that are not collected in conventional RCTs." Even then—before "big data" became a buzzword—folks were aware that data are the raw materials and are shaped into insights and evidence for decision making, such as HTA. We have also seen the emergence of "data science" as a distinct academic discipline. Currently, we are increasingly seeing big data as an essential mechanism for generating RWE, which I interpret as "information"—an economic good.

I think it's also worth remembering that this was occurring amid calls in 2006 by Dr. Gail Wilensky for a national center for comparative effectiveness research (CER) in the US. This led to several CER projects under the American Recovery and Reinvestment Act in 2009 and then to the formation of the Patient-Centered Outcomes Research Institute (PCORI) under the Affordable Care Act in 2010. In my view, RWE is a key aspect of CER—in addition to including the appropriate comparators.

With regard to HTA and RWE, I think we all recognize that when we decide on whether to include another medicine, device, procedure, or other technology in the health benefit package available to plan members, we would like for that decision to be based on a solid projection of the real-world impacts on plan costs and members' health. RWE is essential for that.

HTA bodies also recognize that for medicines the limited data available at product launch make it difficult to accurately assess long-term cost-effectiveness (ie, to compare proposed price with projected health gains). As more RWE is generated over the product life cycle, it obviously makes sense to re-evaluate the value proposition and the price being paid.

What are the benefits of RWE? Are there clear advantages for RWE?

We all are aware of the strengths and weaknesses of randomized controlled trials (RCTs). If done well, they can be superb at dealing with the issue of bias in the treatment effect (i.e., selection bias).

But, at least for the registration drug trials that are done, they may have limited generalizability to real-world decision making because of their inclusion-exclusion criteria, choice of comparator, short duration, or cross-over study design. Thus, how well the trial-based clinical efficacy predicts real-world effectiveness is often unclear.

Ultimately, we do care about real-world effectiveness—and cost-effectiveness—when it comes to HTA. I would say that we have a bit of a schism in our field with some very strong proponents of RCTs and some very strong proponents of RWE for reasons of generalizability. I tend to approach this more from a Bayesian or modeling perspective that integrates my "prior" mental model—based on historical analogies, causal assumptions, target product profile, etc—with RCT results and RWE. The parameters of this updated model are distributions, reflecting uncertainty. More information—from both RCTs and RWE—can be valuable to reduce this uncertainty. As was emphasized by another ISPOR task force, performance-based risk-sharing arrangements can be seen as an investment in RWE to reduce uncertainty.

Our field's focus on the incremental impact of medical technologies—and new medicines in particular—tends to seduce us into thinking that we know more than we do. Because of the regulatory requirements for new medicines, we have a lot more RCT data than almost any other field. But medicines are only 10-15% of healthcare spending in the United States. We have very little RCT data on the 60-70% that is physician and hospital care. So, expert experience and judgment are often used as the evidence to develop guidelines for a large share of healthcare consumption.

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With our cost-effectiveness analyses and budget impact analyses, we ideally would be trying to get an idea of how introducing a new medicine or other technology into the healthcare system would change the general equilibrium of the system. The recent Second US Panel on Cost-Effectiveness in Health and Medicine brings this out in their broader-than-traditional societal perspective. In practice, we are usually doing a straightforward partial equilibrium analysis, which is useful in many instances. We produce a projection of "cost-effectiveness" (emphasizing that effectiveness means "real-world" performance) and a projection of the incremental cost per member per month, holding constant the rest of the health system and economy. Generally, however, we do not prepare a full health system impact model that projects uptake and cost-effectiveness for all of the relevant health plan subpopulations and the related impact on the non-health sector. Still, we are in much better position to predict the system impact of introducing a new medicine than, say, a new physician payment scheme.

Do we need more RWE?

All of us are patients at some point, even if only for minor conditions. Imagine that you have sprained ankle. But when you go the Internet for guidance on how long and how many times to put ice on that ankle, you find some recommendations, but you can't really find any evidence to back them up.

I like to emphasize that information is a public good, whether it is information about the chemical structure of a medicine or information about how that medicine performs in the real world. As common sense and economic theory confirm, free markets tend to undersupply public goods; hence, we need government interventions such as intellectual property rights, (eg, patents, and subsidized research via agencies like PCORI). Of course, there is potential "government failure" as well as potential market failures. I think the jury is still out on PCORI's accomplishments, but regardless of that, it's clear to me that we need to spend a lot more on CER than we have allocated to PCORI.

What can ISPOR do to support the production of RWE?

I think we at ISPOR are poised to contribute a lot more in the coming years, building upon what our task forces have already produced.

We have produced task force reports on a wide range of important good practice issues, including, among others, a checklist of observational studies, treatment effects and improving causal inference in non-randomized studies, and assessing the relevance and credibility of observational studies—a joint ISPOR-AMCP-NPC effort in 2014. And our members are involved in important international efforts such as the IMI GetReal project in Europe.

And just last year—10 years after that first report—our joint ISPOR-ISPE Special Task Force on RWE in Health Care Decision Making made great strides in producing recommendations on good procedural practices and on reporting to improve reproducibility and facilitate validity assessment for database studies.

In commenting on these reports, Dr. Sheldon Greenfield emphasized that the wealth of data from observational studies must be an important contributor to the learning healthcare system of the future. Along these lines, I have always liked the quote from Sir Michael Rawlins' "Harveian Oration" that: "Experiment, observation, and mathematics, individually and collectively, have a crucial role in providing the evidential basis for modern therapeutics. Arguments about the relative importance of each are an unnecessary distraction. Hierarchies of evidence should be replaced by accepting—indeed embracing—a diversity of approaches." I couldn't agree more. But there is also clearly a lot more to be done in terms of generating useful RWE and incorporating it appropriately in healthcare decision making.

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