JANUARY/FEBRUARY 2019 VOL. 5, NO. 1

VALUE & OUTCOMES SPOTLIGHT

An ISPOR publication for the global HEOR community

The Opioid Crisis

FEATURING AN INTERVIEW WITH THE FDA'S DOUGLAS C. THROCKMORTON, MD

The Current State of the Global Opioid Crisis
How regulatory initiatives may fuel illicit use, and how real-world evidence may inform better solutions.

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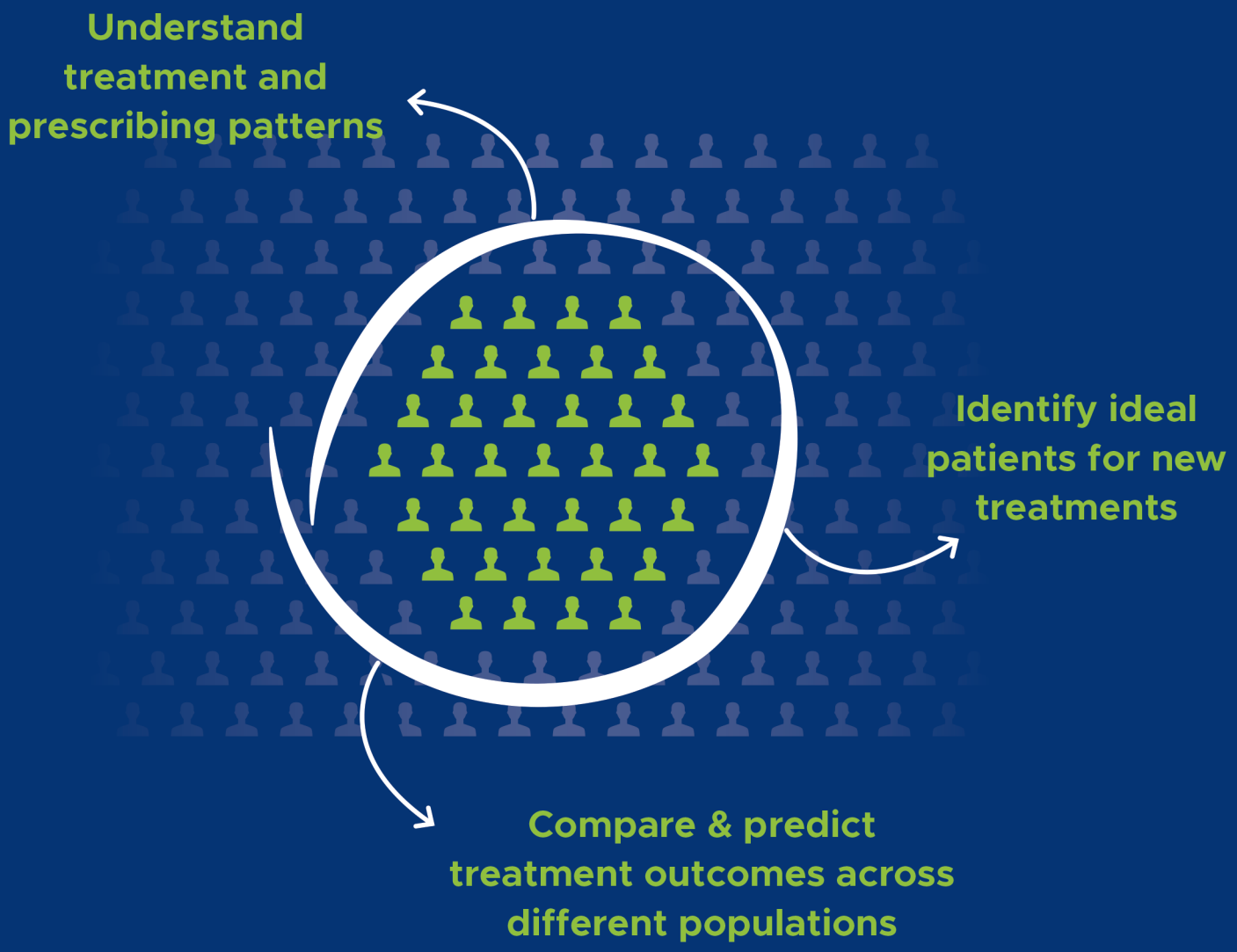

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VALUE & OUTCOMES
SPOTLIGHT

JANUARY/FEBRUARY 2019
VOL. 5, NO.1

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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

With this issue, *Value & Outcomes Spotlight* ushers in in its fifth year of existence with a bang! Our theme is the opioid crisis—its increasingly global spread, its dramatic health and economic consequences, its recalcitrance in the face of increasingly widespread efforts to bring the epidemic to a halt.

The US Food & Drug Administration (FDA) has made combating the opioid crisis its top priority since the appointment in mid-2017 of Scott Gottlieb, MD as FDA Commissioner. In his nomination approval hearings before congress, Dr. Gottlieb went so far as to equate the public health consequences of opioid addiction to those of the Ebola and Zika viruses, and he went on to say that FDA was "complicit, even if unwittingly" in fueling the opioid epidemic.

Value & Outcomes Spotlight reached out to FDA and they agreed to an interview on this subject. So in addition to our feature article on the opioid crisis, a related infographic with notable statistics courtesy of the ISPOR Student Network, and a member profile on one researcher's analyses of the cost-effectiveness of efforts to treat opioid addiction, we have a Q&A with a representative of the one institution that has the most leverage to potentially bring this public health crisis under control.

This is what we mean by starting off the year with a bang.

But that's not all. Our ISPOR Central section contains an article by ISPOR CEO Nancy Berg, in which she reflects on our Society's progress to date and looks forward to the accomplishments to come. ISPOR is in the midst of an update to its strategic plan and making sure this dovetails with the annual business plan is where the rubber hits the road for sustained success. That section also contains a considerable amount of information on ISPOR's conference and education programs, including some facts & figures on membership and short course attendance as well as a map of all five planned 2019 ISPOR meetings. A "Come to New Orleans" article is included to highlight the host city of ISPOR 2019.

Finally, this issue includes three interesting HEOR articles covering an array of topics. The first provides a thoughtful background on opportunities and challenges associated with expansion of network meta-analysis from randomized controlled trials alone to other study designs, specifically those commonly used to generate real-world evidence—as you can imagine, it's not straightforward but techniques are being developed to make this happen. The second piece outlines the fundamentals of real-world evidence generation and use for medical devices, beginning with the most basic concepts and ending with implications for devices joining in on "the internet of things." The third article contains survey data eliciting opinions from patient advocacy groups and HEOR researchers on how best to incorporate the voice of the patient in our studies.

So our Society is off to a strong start and *Value & Outcomes Spotlight* is doing its best to keep up.

Happy reading!

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

ISPOR SPEAKS

Milestones of the Past and a Path for the Future

Nancy S. Berg, CEO and Executive Director, ISPOR, Lawrenceville, NJ, USA

The start of a new calendar year transitions us from acknowledging ISPOR's 2018 successes to a sharp focus on our future Society goals and objectives. Looking back, the Society marked several milestones in 2018. For example, this past year was a record-breaking year for ISPOR's conferences. Attendance at the ISPOR Asia Pacific 2018 conference in Tokyo was up more than 24% from its previous meeting, and the ISPOR Europe 2018 conference in Barcelona attracted the largest audience (5500+) ever at an ISPOR event. All the 2018 ISPOR conferences reflected the new ISPOR branding, which received several industry awards and, most importantly, was embraced by our members.

In addition, I am pleased to report that ISPOR reinvested more than $2.9 million in mission-critical initiatives (ie, education, professional development, travel grants, etc) in 2018 alone as part of its mission to promote health economics and outcomes research (HEOR) excellence to improve decision making for health globally. Our Society continues to lead the field with new initiatives that delve into emerging topics (ie, Real-World Evidence Summit, Health Technology Assessment Central website (www.htacentral.org), the new Patient Council, etc) and produce high-impact journals and award-winning reports (eg, Good Practices for Outcomes Research reports, Top 10 HEOR Trends report) that advance the science, the understanding, and the use of HEOR methodologies to a wider audience.

As we move into 2019, ISPOR is well positioned to build on these successes to advance the field and to continue to deliver value to its members. This year, ISPOR will focus on several important initiatives, namely finalizing the update of its Strategic Plan and implementation of our 2019-2020 Business Plans.

ISPOR STRATEGIC PLAN

ISPOR leaders and members routinely engage in a strategic planning process designed to ensure the organization is forward thinking, positioned for growth, and delivering value to its members and stakeholders. In 2018, a Strategic Plan Work Group was assembled to review progress and update ISPOR's current Strategic Plan (launched in 2016). This working group (which includes participation by members from every stakeholder group and every region) has examined the Society's current position, evaluated opportunities for development, and identified areas for growth and expansion. Our planning process focused considerable attention on ISPOR's organizational positioning, how we view the future of HEOR, and the increasingly influential role that HEOR plays throughout healthcare systems.

A major aim of the Strategic Plan update is to identify ways to deliver even greater value for members in the programs and services we offer. Key elements in our success will be to partner with like-minded organizations on important health policy initiatives and to continue to be a leading force on issues that advance the field to improve healthcare decisions. In the first quarter, the working group will be putting finishing touches on a position paper that more clearly conveys our envisioned future and demonstrates the importance of the work of our members and the Society.

The Strategic Plan Work Group is chaired by William H. Crown, PhD, Chief Scientific Officer at OptumLabs, Cambridge, Massachusetts, USA. The updated Strategic Plan will be presented during the ISPOR 2019 annual conference in New Orleans (May 18-22, 2019).

STRATEGIC PLAN IMPLEMENTATION THROUGH ANNUAL BUSINESS PLANS

To implement its Strategic Plan, ISPOR develops business plans that direct the operation, scientific and educational programs, and special strategic initiatives of the organization. ISPOR's multiyear strategic initiatives are discussed on the website—I encourage every member to take a few minutes to read about them here (www.ispor.org/strategic-initiatives).

HIGHLIGHTS OF 2019 BUSINESS PLANS INCLUDE:

- Identifying, measuring, and communicating the impact that ISPOR is making on healthcare decisions. Our goal is to demonstrate how decision makers and stakeholders in the field are using ISPOR Good Practices for Outcomes Research reports and other resources. >

- Expanding and diversifying member involvement. In addition to writing and adopting a formal statement on diversity, ISPOR will be inviting and recruiting more volunteers to guide activities.

- Continuing to develop and host leading scientific programs around the world. In 2019, major events will be produced in Europe, Latin America, and North America. Also new for 2019 is a regional meeting in Warsaw (March). Another ISPOR Summit is being planned for later this year, as well as HTA Roundtables, Patient Representatives Roundtables, and many other stakeholder meetings that will be held around the globe.

- Initiating programs and member group development in new areas like digital technologies, medical devices, real-world evidence, patient preferences, patient-reported outcomes, universal health coverage, and others.

- Refining our benefits, services, processes, and systems to ensure ISPOR's infrastructure is both contemporary and well-functioning.

We added a *Get Involved* section to the website last fall (www.ispor.org/get-involved). I encourage members to explore all the ways they can engage with the Society to make the most of their member experience. Together we can reach new milestones that spark the imaginations of future generations and drive the field of HEOR.

HEOR NEWS

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

1 The Contribution of New Product Entry Versus Existing Product Inflation in the Rising Costs of Drugs

(*Health Affairs*)

Academics from the University of Pittsburgh show in a new study published in the journal *Health Affairs* that even older drugs are seeing big price hikes, but these increases are driven by the newer drugs entering the market. Brand-name drug price increases are being driven by inflation. "Prices are increasing because the market is bearing it," study lead Inmaculada Hernandez, an assistant pharmacy professor at Pitt, told Vox.

https://www.healthaffairs.org/doi/abs/10.1377/hlthaff.2018.05147?journalCode=hlthaff

2 What Can Pharma Expect in 2019?

(eyeforpharma)

According to experts at eyeforpharma, drug pricing and the affordability of healthcare, centered in the United States but ranging across the globe, is the number 1 issue the pharmaceutical industry will be grappling with in 2019. Industry executives say money will be shifted away from acute care to social care, accompanied by a push for creative pricing models and a need to demonstrate the sustained value of pharma's products.

http://social.eyeforpharma.com/commercial/what-can-pharma-expect-2019

3 Five Innovation Trends That Will Impact the Healthcare Industry in 2019 (*MedCity News*)

The behavioral health epidemic (mostly about opioids but also including eating disorders, anxiety, and depression), artificial intelligence, and more procedures being done in outpatient settings are some of the key 2019 trends that will determine how decision makers purchase technology.

https://medcitynews.com/2018/12/five-innovation-trends-that-will-impact-the-healthcare-industry-in-2019/

4 Lilly to Disclose More Information About Drug Pricing

(*Indianapolis Business Journal*)

On January 8, Eli Lilly & Co started airing television ads touting the website lillypricinginfo.com, along with a toll-free telephone number. The site has information about drug list prices, patient assistance programs, and average patient cost for medicine.

https://www.ibj.com/articles/71968-lilly-to-disclose-more-information-about-drug-pricing

5 Value-Based Oncology Care Delivery Falls Short of Addressing Patients' Psychosocial Needs

(*Oncology Nursing News*)

Ellen Miller-Sonnet, chief strategy and policy officer for CancerCare, shares results of a study she and her colleagues did looking at the experiences, perceptions, and attitudes of more than 3000 people in the United States diagnosed with cancer. The findings highlight significant gaps in the delivery of psychosocial care from diagnosis through survivorship. "Most value-based care approaches underrepresent the long- and short-term interests of patients, for whom value includes but extends far beyond dollar costs," Miller-Sonnet says.

https://www.oncnursingnews.com/advocacy/cancercare/value-based-oncology-care-delivery-falls-short-of-addressing-patients-psychosocial-needs

6 Cost-Effectiveness of Alirocumab: A Just-in-Time Analysis Based on the ODYSSEY Outcomes Trial

(*Annals of Internal Medicine*)

Dhruv S. Kazi of Beth Deaconess Medical Center in Boston and coauthors from the University of California in San Francisco published a decision analysis of the ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab) trial in the *Annals of Internal Medicine*. Using the Cardiovascular Disease Policy Model and data from data sources representative of the United States combined with data from the ODYSSEY Outcomes trial, the authors concluded that "The price of alirocumab would have to be reduced considerably to be cost-effective."

http://annals.org/aim/article-abstract/2719987/cost-effectiveness-alirocumab-just-time-analysis-based-odyssey-outcomes-trial#

7 California Governor Signs Order to Tackle Drug Prices in First Act (*Insurance Journal*)

Reuters reports that the first action of California Governor Gavin Newsom on January 7 was to sign an executive order that could dramatically reshape the way prescription drugs are paid for and acquired in the most populous US state.

https://www.insurancejournal.com/news west/2019/01/08/ 514198.htm

8 The Demand for Real-World Evidence in a Changing Oncology Landscape (Aptitude Health Blog)

According to experts at Aptitude Health, oncologists in the United Kingdom are using "creative health-related activities to generate real-world data and make them available for research without conceding patient confidentiality." The alternate approach being developed is using a simulated data set that contains the same indicators and same data structure as the original set, but no actual patient data.

https://www.aptitude-health.com/blog/demand-real-world-evidence-oncology/

9 Medical Affairs: Future Custodians of Digital Health?
(*Elevate* Magazine)

Alex Butler, cofounder of Foundry, says the future value of digital is going to be the use of technology to improve clinical outcomes and patient outcomes and to help healthcare professionals improve the provision of care. He contends that the future custodians of most of the high-level digital investment in health solutions will be pharma companies' medical affairs departments and says they must take an active interest in driving the strategy and the implementation of these programs.

http://maps.instantmagazine.com/publications/elevate-magazine-issue3/medical-affairs-future-custodians-of-digital-health/

10 10 Things You Should Know About Medicine Spending and Costs (PhRMA's Catalyst Blog)

While prices on many drugs went up on January 1, 2019, PhRMA's Holly Campbell reiterates the industry's commitment to "working with policymakers on solutions that enhance the competitive marketplace, lower costs for patients, and promote continued medical innovation," and provides some real statistics about medicine costs. For example, competition from generics and biosimilars is expected to reduce US brand sales by $105 billion from 2018 to 2022, and hospitals mark up medication prices, on average, nearly 500%.

https://catalyst.phrma.org/10-things-you-should-know-about-medicine-spending-and-costs

11 Impact of Prescription Drug Costs on Health Insurance Premiums (State of Vermont Green Mountain Care Board)

A report from the Green Mountain Care Board says prescriptions—with specialty drugs leading the way—were responsible for nearly 16% of premiums in 2018 for 3 of Vermont's insurers: Blue Cross and Blue Shield of Vermont, MVP Health Care, and the Vermont Health Plan. The study does not factor in rebates and discounts offered by drug manufacturers, and it examines only plans regulated by the care board.

https://legislature.vermont.gov/assets/Legislative-Reports/Act-193-Report-Impact-of-Prescription-Drug-Costs-on-Health-Insurance-Premiums.pdf

12 Building a Real-World Evidence Platform on AWS
(AWS Big Data Blog)

This post from Amazon Web Services (AWS) dates from 2017, but as the challenge of how to integrate real-world evidence grows, the information about how to construct a "data lake" is timely. "Data lakes allow organizations to store all their data, regardless of data type, in a centralized repository. Because data can be stored as-is, there's no need to convert it to a predefined schema. And you no longer need to know what questions you want to ask of your data beforehand. You can use data lakes for ad hoc analyses, so you can quickly explore and discover new insights without needing to structure the data first, as you would with a traditional data warehouse," says Aaron Friedman of AWS.

https://aws.amazon.com/blogs/big-data/building-a-real-world-evidence-platform-on-aws/?_lrsc=dde351b1-6c12-4bd9-a058-b3ae8434bd3f

Progress Through Submissions.

Why Submit an Abstract?

Reach a Global HEOR Audience

ISPOR conferences draw thousands of attendees from the global HEOR community, including researchers, regulators, payers, decision makers, and global thought leaders.

Advance the Science

Contribute your research, ideas, and knowledge to advance the science of HEOR.

Optimize Your Research Impact

Optimize the impact of your research by submitting to an ISPOR conference with its impressive attendee profile, the Society's global recognition, and wide-spread dissemination of conference content.

Advance Your Career

Be part of this international network, become eligible for presentation awards, and be cited in ISPOR's leading HEOR journal, the MEDLINE®-indexed *Value in Health* (all accepted and presented research published online).

What Type of Content Can Be Submitted?

Research Abstracts

Outcomes research on all healthcare interventions, diseases, or methodologies.

Issue Panel Proposals

Issue panel presentations are designed to debate or discuss multistakeholder perspectives on new or controversial issues in HEOR, or its use in healthcare decision making.

Workshop Proposals

Workshop presentations discuss new and innovative applications in the conduct and use of HEOR, real-world data, healthcare policy, and clinical-, economic-, patient-reported-, or patient-preference outcomes.

For more information on abstract submissions, including instructions, examples, and specific evaluation criteria, please visit www.ispor.org.

CONFERENCES & EDUCATION

Progress Through Partnerships.

Partnering with ISPOR provides the perfect opportunity to meet, network, and collaborate with influencers in the HEOR community including decision makers, regulators, payers, researchers, and patient representatives. There are many ways to begin or expand your partnership with ISPOR:

SPONSORED EDUCATIONAL OPPORTUNITIES

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Forums

Webinars

Training Programs

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Institutional Council Membership

Patient Representative Roundtable

Travel Grants

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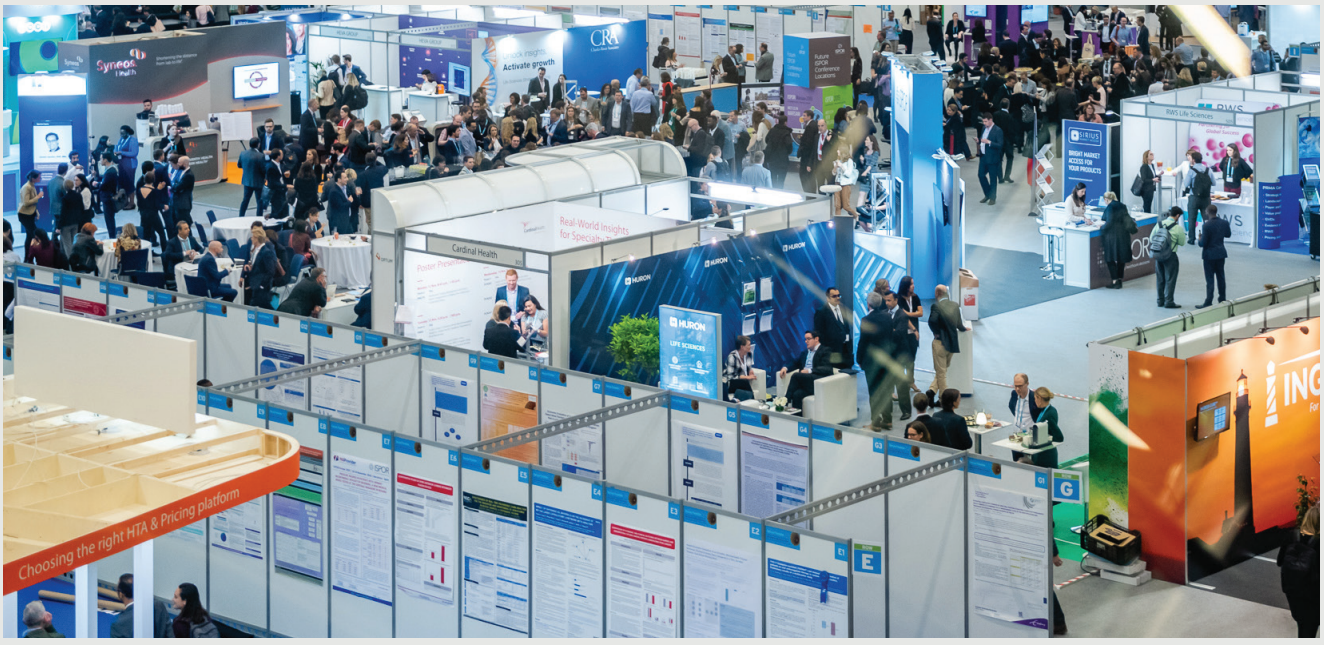
Coffee Breaks

Registration Bags

Notebooks

And more...

For details on how you, or your organization can become involved, please contact: exhibit@ispor.org



ISPOR 2018 Year in Review

Investing in the Future

$2.9 million USD

Mission Critical Initiatives

Membership

20,000 Individual & chapter members

115 Student chapters

86 Regional Chapters

Conferences*

11,335 Registrants

116 Countries Represented

179 Exhibitors & Sponsors

5000+ Presentations

*Totals are cumulative of 2018 ISPOR conferences: ISPOR 2018, ISPOR Asia Pacific 2018, ISPOR Dubai 2018, ISPOR Scientific Summit 2018, ISPOR Europe 2018.

HEOR Education

5042 Course registrations

79 Course topics

20 New short courses

2 New training programs

Publications: Value in Health

5.494 Impact factor

3rd/79 Health Policy & Services journals

6th/353 Economics journals

3rd/94 Healthcare Science & Services journals

Special Initiatives

Women in HEOR | Real-World Evidence | Health Technology Assessment | Patient Engagement

CONFERENCES & EDUCATION

Join us for ISPOR'S 2019 Conferences!

ISPOR Warsaw 2019

Warsaw, Poland
27-28 March 2019

Early Registration Deadline:
26 February 2019

ISPOR 2019

New Orleans, LA, USA
May 18-22, 2019

Abstract Acceptance Notification:
March 1, 2019

Early Registration Deadline:
April 9, 2019

Pre-meeting HEOR Short Courses Offered

ISPOR Latin America 2019

Bogotá, Colombia
12-14 September 2019

Abstract Submissions Close:
13 March 2019

Abstract Acceptance Notification:
1 May 2019

Early Registration Deadline:
30 July 2019

Pre-meeting HEOR Short Courses Offered

ISPOR Scientific Summit 2019

Baltimore, MD, USA
October 11, 2019

ISPOR Europe 2019

Copenhagen, Denmark
2-6 November 2019

Abstract Submission Opens:
1 March 2019

Abstract Submissions Close:
12 June 2019

Abstract Acceptance Notification:
1 August 2019

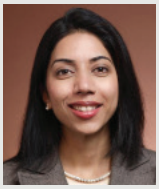
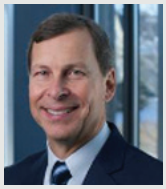
Early Registration Deadline:
24 September 2019

Pre-meeting Short Courses Offered

For more information and registration: **www.ispor.org**

CONFERENCES & EDUCATION

"Rapid. Disruptive. Innovative." A Perfect Melding of ISPOR 2019's Theme and Location


Jalpa A. Doshi, PhD, University of Pennsylvania, Philadelphia, PA, USA; **Brian O'Rourke, PharmD**, Canadian Agency for Drugs and Technologies in Health, Ottawa, ON, Canada; **Rosanna Tarricone, MSc, PhD**, Bocconi University, Milan, Italy

Dear Colleagues and Friends,

We are very pleased to invite you to join us in New Orleans for ISPOR 2019, the leading global conference for health economics and outcomes research (HEOR). Given the continual shift in the healthcare landscape worldwide, this year's theme, "Rapid. Disruptive. Innovative: A New Era in HEOR," is especially timely. Constant change is the new normal. Rapid advances in information technology, medical technology, and treatments targeted at using the body's own genetic and immune systems to fight disease, combined with transformation in regulatory decision making, health insurance, and payment and delivery systems, raise vital questions that will be addressed in plenary sessions, issues panels, workshops, and research presentations. The plenary sessions will focus attention on the emerging challenges of disruptive technology in healthcare, including how trade-offs in speed to market need to balance with continued focus on safety and how to promote affordability and equity of access while continuing to encourage life-changing innovative research and development.

The first plenary on Monday, May 20, "The Dawn of Disruption in the Health Sector: Will Innovative Technologies Require Innovative Ways of Thinking?," will examine the promise and challenge of exciting new medical technologies currently under development. This plenary session will begin with an overview of the current and future landscape followed by a discussion among leading experts. Emerging challenges and opportunities presented by disruptive technologies will be addressed from the perspective of a variety of stakeholders such as payers, manufacturers, and patients.

The second plenary on Tuesday, May 21, "No More *J'accuse*: How Do We Prevent Another 'Implant Files' Case in The Medical Devices Sector?," will consider the balance between the necessity of getting much-needed medical advances to patients and the ability to discern safety issues based on clinical evidence available at the time of regulatory submission. This plenary will start by reviewing these issues, followed by a discussion among major stakeholders that will bring their perspectives on what can be done to improve regulation systems.

The third and final plenary session—on Wednesday, May 22—"Is Affordability Driving a Need to Revolutionize Drug Pricing?," debates the issue of appropriately rewarding pharmaceutical innovation while recognizing that current pricing and coverage/reimbursement mechanisms may be hindering access for the very patients who desperately need these treatments.

These plenaries, along with our outstanding short-course program, topical issue panels and workshops, and research presentations guarantee a worthwhile experience and an international perspective for all conference attendees.

Along with an outstanding scientific program, we also encourage you to join us at ISPOR 2019 to experience the vibrant city of New Orleans, where ISPOR returns for the first time since 2013. Affectionately named the "Big Easy," New Orleans is sure to provide plenty of opportunities to relax and unwind after a day of scientific sessions and canvassing the poster/exhibit hall.

New Orleans is known for its unique cuisine, which reflects its history as a melting pot of French, African, and American cultures. You will have no trouble finding a good bowl of gumbo, delicious beignets, and jambalaya. There is plenty of nightlife, most notably the bustling Bourbon Street, a terrific live music scene (especially for jazz aficionados), and can't-miss stops such as the famous French Quarter. Unfortunately, we will arrive in New Orleans too late to experience Mardi Gras, but it could be worth a return trip to enjoy the event known for costumed parades and street parties.

See you in the "Big Easy"!

FROM THE JOURNALS

Value in Health January 2019

THEMED SECTION: EUROQOL

Overview, Update and Lessons Learned from the International EQ-5D-5L Valuation Work: Version 2 of the EQ-5D-5L Valuation Protocol

Elly Stolk; Kim Rand; Kristina Ludwig; Barend Van Hout; Juan Ramos-Goni

The authors present the challenges faced in EQ-5D-5L valuation since 2012 and how these were resolved and describe in depth a set of new challenges that have become central in currently ongoing research on how EQ-5D-5L health states should be valued and modeled.

Cost-Utility Analysis Using EQ-5D-5L Data: Does How the Utilities Are Derived Matter?

Fan Yang; Nancy Devlin; Nan Luo

The author explores how the use of EQ-5D-5L value set and crosswalk from EQ-5D-5L to EQ-5D-3L (and use of 3L value set) would affect cost-effectiveness analysis results for England and six other countries (Canada, the Netherlands, China, Japan, South Korea and Singapore).

HEALTH POLICY ANALYSIS

Identifying the Need for Good Practices in Health Technology Assessment: Summary of the ISPOR HTA Council Working Group Report on Good Practices in HTA

Finn Boerlum Kristensen; Don Husereau; Mirjana Huic; Michael Drummond; Marc Berger; Federico Augustovski; Ken Bond; Uwe Siebert; Andrew Booth; John Bridges; Jeremy Grimshaw; Maarten Ijzerman; Daniel Ollendorf; Alric Ruether; Jitender Sharma; Allan Wailoo; Egon Jonsson

The authors findings suggest that although many good practices have been developed in areas of assessment and some other key aspects of defining HTA processes there are also many areas where good practices are lacking.

FOR MORE INFORMATION
Visit: https://www.ispor.org/publications/journals/value-in-health.

Value in Health February 2019

BRIEF REPORT

The Internal Validity of Discrete-Choice Experiment Data: A Testing Tool for Quantitative Assessments

F. Reed Johnson, Jui-Chen Yang; Shelby Reed

In this article, the authors develop a tool for testing internal validity of discrete-choice experiment data, deploy the program, and collect summary test results from a sample of active health researchers to demonstrate the practical utility of the tool in a wide range of health applications.

HEALTH POLICY ANALYSIS

Was It Worth Introducing Health Economic Evaluation of Innovative Drugs in The French Regulatory Setting? The Case of New Hepatitis C Drugs

Valerie Clement; Veronique Raimond

This article constitutes the first attempt to draw lessons from the recent uptake of health economic evaluation of innovative drugs in the French regulatory framework.

PATIENT-REPORTED OUTCOMES

Perceptions of Response Burden Associated with Completion of Patient-Reported Outcome Assessments in Oncology

Thomas Atkinson; Carolyn Schwartz; Leah Goldstein; Iliana Garcia; Daniel Storfer; Yuelin Li; Jie Zhang; Bernanrd Bochner; Bruce Rapkin

The authors sought to quantify patient response burden and identify its predictive factors.

The current state of the global opioid crisis.

AS OPIOID MISUSE BECOMES A GLOBAL EPIDEMIC, REAL-WORLD EVIDENCE MAY HELP TO INFORM TREATMENT GUIDELINES SO AS TO ACHIEVE SAFER AND MORE EFFECTIVE PRESCRIBING BEHAVIORS, ESPECIALLY IN CHRONIC PAIN SUFFERERS.

By Michele Cleary

INTRODUCTION

The pernicious opioid crisis is rapidly spreading worldwide. As stakeholders are taking bold steps to contain this epidemic, approximately 27 million people globally are suffering from opioid use disorders.[1] Paradoxically, efforts designed to stem the epidemic's growth may now be fueling its spread. Chronic pain sufferers, faced with firm prescription limits, are finding relief with illicit opioids, while regulations are pushing opioid manufacturers into previously under- supplied markets in developing nations.

Between the overuse of prescription opioids and the worsening spread of illicit opioids, we are facing a global health crisis. As policy makers, clinicians, and other stakeholders initiate new treatment guidelines, laws, and regulations, health economics and outcomes research (HEOR) professionals must consider how we can contribute to the search for solutions to ensure ethical pain management for those in need.

OPIOIDS AS PROACTIVE PAIN MANAGEMENT

The opioid crisis began in the 1990s, stemming from a legitimate concern that many patients were living with unacceptable levels of pain. In the United States, The Joint Commission—formerly The Joint Commission on the Accreditation of Healthcare Organizations or JCAHO—characterized pain as the "fifth vital sign." Medical and patient associations advocated for a more proactive approach to pain management, encouraging broader use of opioids for pain management to address the epidemic of untreated pain.[2]

These changes in the perception of pain management coincided with the release and intensive promotion of OxyContin (oxycodone). Equipped with only minimal pain management training, many providers began prescribing opioids beyond palliative care to patients with chronic, nonmalignant pain, despite a lack of supporting evidence of their effectiveness.[3] >

These conditions fostered a flurry of opioid prescribing. Between 1991 and 2009, the number of opioid prescriptions filled in the United States tripled, reaching prescribing levels sufficient to medicate every citizen continuously for a month. In 2014, opioids became the most frequently prescribed medications in the United States, making the country the global leader in prescription opioid use, consuming 80% of the global supply of opioids, despite accounting for less than 5% of the world's population.[4]

THE SHORT PATH FROM PRESCRIPTION OPIOID USE TO MISUSE AND ABUSE

As has been well documented, rampant prescription opioid use often leads to opioid misuse and abuse of prescription—and sometimes illicit—opioids. Up to a quarter of long-term prescription opioid users treated for chronic nonmalignant pain battle opioid addiction, often leading to future illicit opioid use and overdose.[5]

This descent into illicit drug use is often based in misguided attempts to manage pain. In a 2014 survey of people undergoing treatment for opioid addiction, 94% of respondents said they turned to heroin because prescription opioids were more expensive and harder to obtain.[6]

Between 1991 and 2009, the number of opioid prescriptions filled in the United States tripled, reaching prescribing levels sufficient to medicate every citizen continuously for a month.

THE STAGGERING HUMAN COSTS OF THE OPIOID CRISIS IN THE UNITED STATES

The costs of opioid misuse and abuse have been staggering. Since 2000, more than 600,000 Americans have died from opioid-related drug overdoses, eclipsing the total number who died in World Wars I and II combined. In 2016 alone, 42,000 Americans—an average of 116 every day—died from opioid overdose.[7] Roughly half of these deaths involved a prescription opioid. Yet as staggering as these totals are, opioid-related overdose deaths may be dramatically undercounted. Some have suggested that the actual number of opioid-related deaths may be 24% higher than previously reported.[8]

Even with possible undercounting, "opioid overdose" has become the leading cause of accidental death in the United States, contributing to a drop in life expectancy for the third year in a row. This marks the first time that this country has witnessed a three-year continuous drop in life expectancy since the early 20th century when the nation was in the throes of World War I and the Spanish Flu epidemic of 1918.[9]

Beyond the pain and suffering stemming from opioid misuse, the economic costs have been monumental. The White House Council of Economic Advisers places the economic burden of opioid misuse at more than $500 billion, roughly 2.8% of gross domestic product.[10]

THE EPIDEMIC SPREADS

Rampant opioid misuse is now plaguing Canada, Australia, and parts of Europe.

Canada is now the world's second largest per capita consumer of prescription opioids. The number of prescriptions written for oxycodone increased in Canada by 850% between 1991 and 2007. And as with the United States, the aggressive prescribing of opioids has led to skyrocketing rates of opioid misuse and abuse. In 2017, nearly 4000 Canadians died as a result of opioids, a 34% increase over the year prior.[11]

Data from Safescript show that in Europe, roughly three-quarters of the continent's 1.3 million high-risk opioid users reside in 1 of 5 countries: Germany, Spain, France, Italy, and the United Kingdom.[12] Prescription rates in Germany have risen to nearly the Canadian level, while the number of opioids prescribed in the United Kingdom doubled between 2006 and 2016. And in Australia, the number of OxyContin prescriptions nearly quintupled between 2001 and 2013.[12]

REINING IN AN EPIDEMIC

Stakeholders worldwide are scrambling to control this health crisis. From the United Nations Office on Drugs and Crime (UNODC) and the European Union Drug Strategy to the US Food and Drug Administration's (FDA) Opioid Policy Steering Committee and the Canadian Drugs and Substances Strategy, regulatory bodies worldwide have all introduced multipronged initiatives to combat the opioid crisis, including strategies designed to prevent new addictions, treat opioid use disorder, develop new pain therapies, and improve drug enforcement.

Other strategies include the Lancet Commission, which recommended closer monitoring of opioid marketing and restrictions on direct marketing of opioid medications to healthcare providers by pharmaceutical companies. And both the FDA and the European Medicines Agency have approved antideterrent formulations.

GROWING CONTROVERSY SURROUNDING OPIOID PRESCRIBING LIMITS

Many physicians have reported feeling that their pain management training has been insufficient to manage pain effectively.[14] In 2016, the US Centers for Disease Control (CDC) released their Guideline for Prescribing Opioids for Chronic Pain to help practitioners deliver ethical and effective pain management for their chronic pain patients.[15] These guidelines joined the World Health Organization (WHO) Cancer Pain Ladder in recommending nonopioids as first-line therapy for patients suffering from chronic pain; both recommended strong opioids only as other nonopioids failed to control pain.

Yet across the United States, state and federal governing bodies have incorporated these pain management guidelines into more concrete prescription limits, taking more aggressive action to minimize patient exposure to opioids and flag possible over-prescribers. Laws in more than half of US states limit acute pain sufferers to only 3 to 7 days of prescription opioids, regardless of the severity of their surgery or injury. Some payers, pharmacy benefit managers (PBMs), and major pharmacy chains also have adopted mandatory restrictions on the opioid prescriptions they will fill, often requiring prior authorizations before filling opioid prescriptions. And on January 1st of this year, Centers for Medicare and Medicaid Services initiated new prior authorization

rules for Medicare that trigger reviews for prescriptions over 200 mg MME (morphine milligram equivalents).

These limits may have contributed to reductions in opioid prescribing rates, which in the United States have fallen to their lowest rates in a decade. However, this trend appears to be due to fewer acute pain prescriptions being filled, as the average number of days supplied increased from 13.3 in 2006 to 17.7 in 2015.[15]

ARE OPIOID PRESCRIBING POLICIES ABANDONING CHRONIC PAIN PATIENTS?

But formalizing opioid prescribing guidelines into strict dosing limits may be jeopardizing the well-being of patients most in need—those in the grips of chronic pain. In the United States alone, approximately 18 million chronic pain sufferers are currently prescribed opioids. While some chronic pain sufferers may be treated effectively within current limits or by using nonopioid therapies, others find that their pain requires more aggressive treatment beyond what many prescription limits allow.

More flexible prescribing limits are needed, as well as better guidance regarding opioid tapering and opioid avoidance. Ideally, guidelines would also address the psychological reluctance felt by patients and providers to accepting opioid reductions.

MEANWHILE, ILLICIT MARKETS GROW

These rigorous dosing limits often treat chronic opioid users as opioid abusers, stigmatizing those patients for whom prescription opioids are both necessary and medically appropriate. Many chronic pain sufferers—even those suffering from malignant pain—fear that opioid prescription limits will lead to the resurgence of uncontrolled pain.[16]

Facing increasingly restricted access to their opioid prescriptions, some chronic pain sufferers are turning to illicit opioids, such as heroin. The illicit market is booming, filled by the rapid proliferation of highly potent, inexpensive synthetic opioids, such as fentanyl or its analogs. Between 2010 and 2016, the United States observed a 546% increase in overdose deaths from synthetic opioids (mostly fentanyl).[18] Meanwhile, fentanyl-related deaths are becoming increasingly common in Canada and across Europe.[11,13]

The fact that in 2018, so many people lack access to the medicines they need while in other parts of the world, the oversupply, aggressive marketing, and excessive prescription practices has led to a fatal opioid overdose crisis is one of the major paradoxes we face. We must find ways of doing better.

REGULATORY PRESSURE PUSHING OPIOIDS INTO NEW MARKETS

The increasingly regulated market for prescription opioids has pushed some opioid producers to other global markets, such as Latin America, Asia, or North Africa—regions that have historically suffered from insufficient access to pain therapies.[19] The global gap in effective pain management and access to prescription opioids has long been an area of concern. Per capita medicinal opioid consumption in many of these regions is far below the International Narcotics Control Board's minimum global standard to meet citizens' palliative care needs (of 200 daily doses per million inhabitants per day). This dearth of effective pain management has led to calls by the United Nations to increase access to opioids for pain management in certain low- and middle-income countries.[19]

In the face of such minimal access to effective pain treatments, pain sufferers throughout these new markets have been highly receptive to new prescription opioids. Prescription opioid sales in Brazil increased 465% between 2009 and 2015. Even China, despite a long, bitter history with opium, is seeing a rapid rise in the number of prescriptions for opioids to treat pain.

RESISTANCE TO THE USE OF GUIDELINES GROWS

This past fall, members of the American Medical Association (AMA) House of Delegates approved a resolution advocating against inappropriate use of the CDC opioid prescribing guidelines for chronic pain. Delegates noted the dangerous impact of some opioid regulations.

The 2017 AMA Prior Authorization Physician Survey found over 90% of doctors believed that limits on prescription days/dosages and prior authorizations negatively impacted patient outcomes. Since the release of the CDC guidelines, chronic pain sufferers are reporting increasing difficulty filling their opioid prescriptions due to these mandated restrictions. Some patients have reported being abandoned by their treating physicians who fear regulatory reprisal for prescribing opioids.

The resolution formally pushes back against the misapplication of the CDC's guideline by regulatory bodies, state medical boards, pharmacists, PBMs, insurers, and others. The resolution argues that the dosage guidance should not be used as a rigid dosage limit or mandate. Some patients require doses higher than those recommended by the CDC guidelines. Furthermore, the resolution asserts that flagging physicians for suspect prescribing—subjecting these providers to potential sanctions—does a tremendous disservice to many chronic pain sufferers by disincentivizing these providers from caring for these patients.

In November 2018, a letter published in *Pain Medicine* expands upon the AMA resolution by suggesting that the risks associated with forced tapering of opioids may do more harm than good.[23] Members of the International Stakeholder Community of Pain Experts and Leaders noted that rapid forced tapering off opioids can destabilize patients, leading to worsening of pain, severe loss of function, and crippling withdrawal symptoms. In the letter, the authors strongly petition for more realistic treatment guidelines that avoid "aggressive and unrealistic" dosing goals.

NEXT STEPS

With persistently high rates of opioid prescribing worldwide, rising nonmedical prescription opioid use, and global opioid market diversification (including the emergence of high-potent, synthetic opioids), a pressing need exists for well-informed policies to prevent further expansion of this opioid epidemic. This will require a thoughtful and coordinated approach focused

not only on evidence-based supply reduction strategies (eg, safer prescribing, curtailment of prescription industry influence), but also on the need for dramatic efforts to implement and scale up public health and addiction treatment interventions globally.

More opioid prescribing guidelines are on the horizon. In October 2018, President Trump signed the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment Act into law, providing additional support to the FDA's current efforts to promote the development of evidence-based opioid prescribing guidelines for treating acute pain resulting from specific conditions or procedures. The FDA enlisted the support of the National Academies of Sciences, Engineering, and Medicine to develop these guidelines by reviewing existing opioid analgesic prescribing guidelines, identifying potential gaps in evidence that informed those guidelines, and specifying any additional research needed to fill these gaps in evidence gaps.

HEOR research will be critical to ensuring that North America's opioid emergency does not foreshadow a global crisis. Real-world evidence (RWE) combined with sound public health policy research can help us learn from past mistakes while informing future steps. Evidence-based guidelines can lead to more appropriate opioid prescribing behavior. Equipped with sound RWE research, stakeholders can develop evidence-based policies to ensure pain patients receive the treatment best suited to their needs—be it an opioid or a non-opioid alternative.

Much rests on these new approaches. As Dr. Viroj Sumyai, president of the United Nations International Narcotics Control Board, reiterated during the Commission on Narcotic Drugs meeting in November 2018:

The fact that in 2018, so many people lack access to the medicines they need while in other parts of the world, the oversupply, aggressive marketing, and excessive prescription practices has led to a fatal opioid overdose crisis is one of the major paradoxes we face. We must find ways of doing better.

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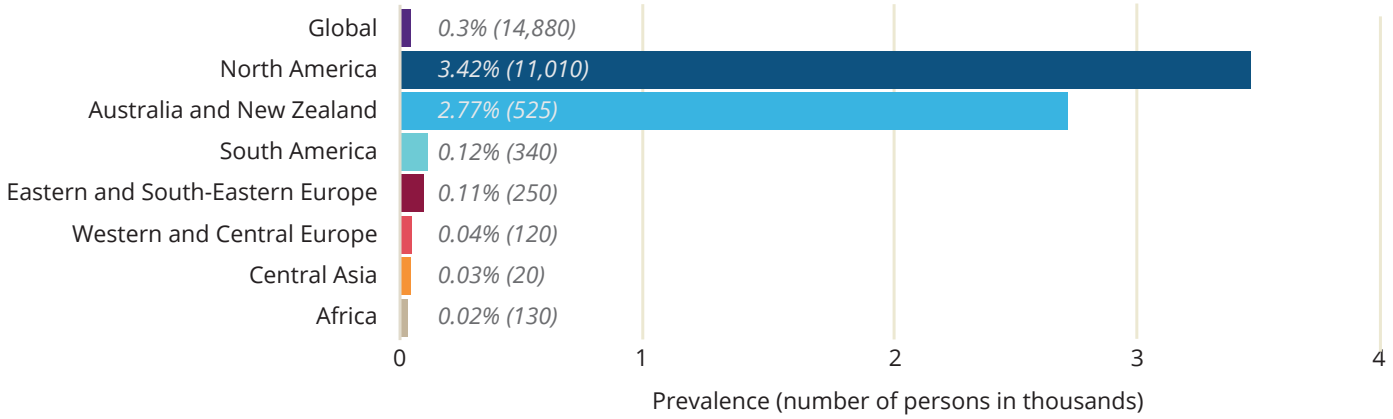
By the Numbers: The Global Opioid Crisis

Section Editor: The ISPOR Student Network

PREVALENCE OF GLOBAL PRESCRIPTION OPIOID USE IN 2016 (MEDICAL AND NON-MEDICAL PURPOSES)[1]

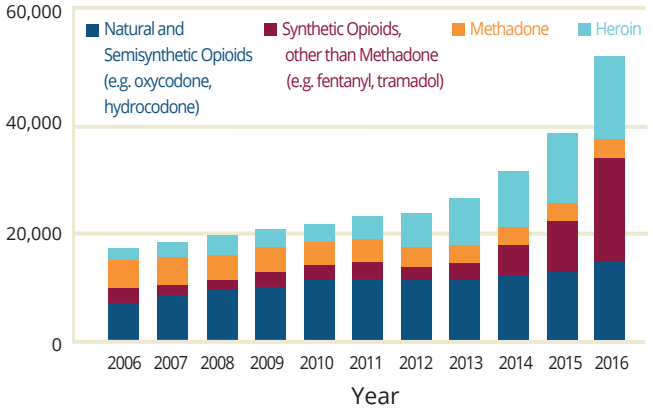


Opioid Prescriptions Dispensed in the United States (2006–2017)[2]

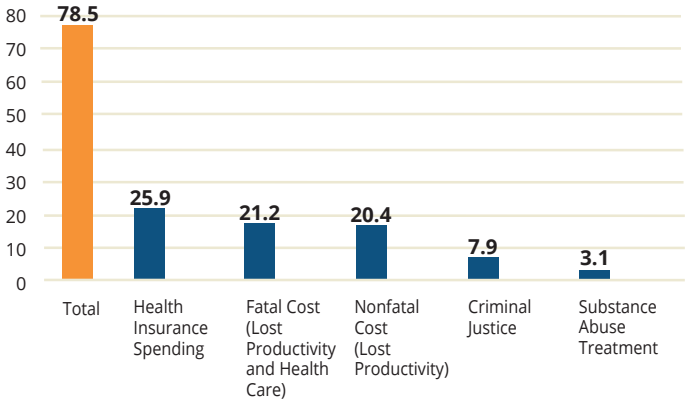
Prescribing Rate per 100 Persons

Opioid Overdose Deaths by Type of Opioid in the United States (2006-2016)[3]

Number of Deaths



Societal Costs of Treating Opioid Disorders in the United States, 2014 (in BIllion USD)[4]



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Is Pharmacotherapy Enough to Manage the Opioid Crisis?

One researcher thinks we could do more by instituting cost-effective behavioral interventions instead.

Bill Padula, PhD, an active long-standing member of ISPOR, is Assistant Professor of Pharmaceutical & Health Economics in the Leonard D. Schaeffer Center for Health Policy & Economics and School of Pharmacy at University of Southern California in Los Angeles, CA, and Principal at Monument Analytics. We caught up with Bill to discuss his cost-effectiveness research on interventions to treat opioid addiction and to hear his thoughts on the opioid epidemic.

VOS: Tell us about your research and how you got interested in the opioid crisis.

Bill Padula: I became interested in identifying high-value interventions to treat opioid addiction based on conversations with some of my colleagues at USC, Johns Hopkins Medicine, and Dartmouth-Hitchcock Medical Center who were addressing the needs of their patients dealing with addiction. These colleagues often said that there are few viable alternatives to opioids for severe pain, so we can't just stop prescribing—and because these drugs are addictive, we need to manage that and find cost-effective approaches to treating addiction.

So what have you found—are current interventions to treat opioid addiction economically viable?

Working with psychiatrists, our research has found that cognitive-behavioral interventions have a net increase on healthcare budgets in budgetary impact analyses, but the spending represents good value for money as the cost-effectiveness (CE) analyses are yielding CE ratios well within the acceptable limits of $100,000 per quality-adjusted life years gained. We've also looked at behavioral interventions in combination with methadone and similarly found these to be cost-effective. One thing you must understand, from a value perspective, is that many addicted individuals lose their jobs, damage their family relationships, and sometimes lead to homelessness. These interventions help restore them to a productive place in society.

You mentioned that clinicians suggest that there are few good alternatives to opioids—are there solutions on that front?

While opioids are likely here to stay, a great deal of improvement can be made in terms of how opioid use is managed. For example, we have not made much effort to date on understanding the minimum threshold for pain management and how opioid use can be limited to achieving that goal. Typically, patients are discharged from the hospital or sent home from a doctor's or dentist's office with a prescription for an opioid, without enough instructions for rehabilitation to minimize the dose. We can definitely do better on that front and can probably take lessons from other countries, where pain is more often tolerated than managed.

Speaking of other countries, are we seeing an opioid epidemic elsewhere or is this strictly a US problem?

This is obviously a huge problem in the United States but not solely there. You really see this also in other industrialized countries, like Canada, and European countries. However, you don't see it is in developing countries, where expectations for patient comfort vis-à-vis pain are very different. We might want to take a lesson from Africa, Latin America, and Southeast Asia, where pain is viewed more as the body's natural response to life encounters as opposed to something that needs to be treated at all costs. Obviously, that's a gross generalization but there's something to it.

Are there any tactics to address the opioid crisis that haven't been leveraged yet?

Machine learning and Big Data are hot in the health economics and outcomes research world right now, and to my knowledge, have not been applied effectively to the opioid crisis yet. Identifying a minimal threshold for pain management with opioids for different patient cohorts/subgroups using pharmacologic methods would be a slow, detailed process looking at one patient at a time.

There is an opportunity to apply machine learning to Big Data to identify minimal opioid amounts used in select patients in cohorts that have led to effective pain management without the need for long-term refills or indicators of addiction. However, machine learning models might be agnostic to factors that differentiate patients with a hereditary predisposition for addiction.

Network Meta-Analysis for Various Study Designs: Stepping Outside the Randomized Controlled Trials Comfort Zone Into the Real World

Andreas Karabis PhD, Real World and Analytic Solutions, IQVIA, Amsterdam, The Netherlands

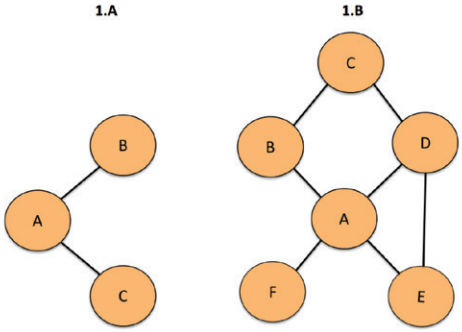
Randomized controlled trials are the dominant type of evidence in network meta-analysis. Appropriate methods for feasibility assessment, analysis, and reporting are essential for the inclusion of real-world evidence in network meta-analyses.

NETWORK META-ANALYSIS: WHAT AND WHY

Evidence from randomized controlled trials (RCTs), collected by means of systematic literature reviews, is routinely used in healthcare decision making, including clinical guidelines and reimbursement. When evidence from more than one RCT comparing the same intervention with the same comparator is available, a quantitative approach called meta-analysis is used to synthesize the results in a single outcome. Meta-analysis was introduced 40 years ago, contributing to the establishment of evidence-based clinical practice.[1]

In many cases, the competing interventions relevant to the decision are more than 2 and are not compared simultaneously in a single RCT. New drugs are often compared only with placebo or standard care, but not against all the alternative interventions of interest. Furthermore, the comparators of interest may vary by country or change over time, making the design of an RCT that includes all the alternatives impractical or not feasible.

Figure 1. Indirect treatment comparison and network meta-analysis



In the absence of RCTs comparing all interventions of interest directly, an indirect treatment comparison (ITC) can provide evidence for the difference in treatment effects.[2] For example, interventions B and C, for which we have only placebo-controlled trials, could be compared indirectly via placebo. This simple network is presented in Figure 1A, where the lines represent head-to-head RCTs.

As an extension of indirect comparison, a network of RCTs could be formed including direct evidence (by means of head-to-head RCTs) and indirect evidence (by means of ITC), in a so-called mixed-treatment comparison (Figure 1B).[3] In line with ISPOR Task Force recommendations, we use the term "network meta-analysis" (NMA) when the evidence network involves more than 2 RCTs and more than 2 interventions.

A valid NMA is based on the assumptions of transitivity (ie, indirect comparison validly estimates the unobserved head-to-head comparison) and consistency (ie, direct and indirect estimates in a network —if available—are in agreement).

THE DOMINANCE OF RCTS AND THE NEED FOR RWE

Although widely accepted and routinely used for decision making, NMAs are often limited to synthesizing evidence from RCTs. Under 4% of the NMAs published until 2014 included designs others than RCTs.[4] This is not unexpected because for decades, the gold standard for evidence generation in medical product evaluation has been the RCT. If designed appropriately and executed as planned, RCTs are expected to provide unbiased results about the effects of alternative interventions.

RCTs have well-known limitations in representing everyday clinical practice, as by definition they are conducted in selected populations and in controlled environments to ensure protocol adherence.

Beyond these fundamental limitations, there are cases where no RCTs are available to support a specific question in healthcare decision making. For example, interventions of interest may not have been studied in RCTs for ethical or other reasons. Also, certain types of effects

cannot be adequately studied in RCTs (eg, safety, long-term outcomes). There also may be cases where the evidence base consists of RCTs that are not adequately designed to address the relevant clinical question.

Even if a properly designed RCT including the interventions, population, and subpopulations of interest is feasible, it can take years from design to completion, while in many cases relevant real-world evidence (RWE) is readily available and can be used to support clinical decisions.

Stepping outside the comfort zone of RCTs is not without challenges, starting with the definitions. An entire universe of study designs are referred to simply as "non-RCTs" or "nonrandomized studies" (NRS). Although the definition of RWE is still evolving, evidence from registry studies, claims databases and administrative data, health surveys, electronic health records, and medical chart reviews is widely accepted as RWE.[5]

However, within the frame of healthcare decision making, NMA is used to estimate the relative effects of interventions. Thus, the main interest regarding RWE is in comparative studies reporting relative treatment effects. When departing from the RCT design, the preferred evidence to be included in an NMA is in the form of well-designed, high-quality cohort studies, case-control studies, and nonrandomized comparative clinical trials, although other study designs may also be considered (Figure 2).[6] Evidence hierarchy, a system of rating the quality of evidence, could be used to navigate through the options.[7,8]

Figure 2. Beyond RCTs

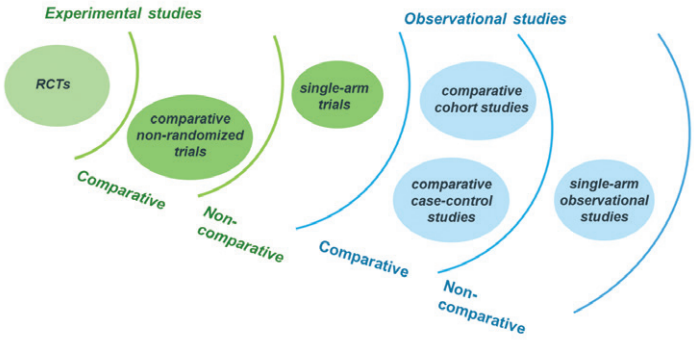
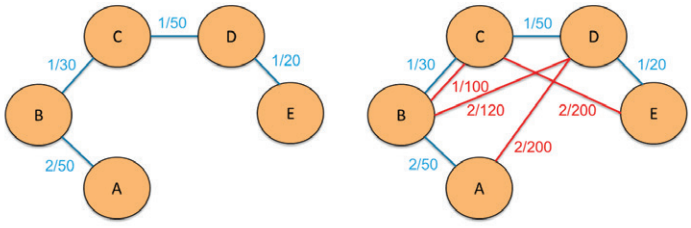


Figure 3. Reducing uncertainty with RWE in case of connected but "weak" networks



Numbers indicate "number of studies/number of participants" of the related comparisons.

The use of RWE is critical in several cases, the most important of which is probably to connect networks. The fundamental assumption of NMA methodology is the existence of a connected network of studies, while lack of RCTs for some of the interventions may lead to a disconnected network. In this case, RWE studies could be used to bridge the gaps and connect the fragmented network.[9] This can also be beneficial in reducing the underlying uncertainty also in the case of connected but "weak" networks (Figure 3) (ie, networks with a small number of RCTs connecting a relatively high number of interventions, networks of RCTs with very low number of randomized patients, or networks of RCTs of extremely poor quality), under certain conditions (eg, agreement between sources of evidence).

HOW CAN THIS WEALTH OF RWE BE USED?

Although inclusion of RWE in an NMA can complement evidence from RCTs or address some of the RCT limitations, thorough review of their quality is necessary. It is well-known that nonrandomized studies are vulnerable to biases, including confounding, thus studies that do not appropriately account for confounding factors may produce biased effect estimates. In this case, the underlying NMA assumption of transitivity may be violated, producing biased estimations for the relative treatment effects.

Before any analysis, the assessment of the quality of RWE should be conducted using appropriate tools, such as ROBINS-I.[10] It is important to ensure that the relative treatment effects in RWE are estimated using appropriate methods to minimize bias.[11] An important indicator of the RWE quality is the agreement between the evidence from RCTs and other study designs that could be easily assessed in a network of interventions connected by both types of studies.

Several methods have been proposed that account for potential bias from RWE in NMA,[6] including:

Design-adjusted analysis: In this approach, each study type can be adjusted separately using a weight w (0<w<1). Setting w=1 means that RWE has the same value as the RCTs (naïve pooling), while setting w=0 means that RWE is ignored. By changing the value of the weight, we can control the confidence we place in RWE. In addition, the point estimate of each study is shifted by a constant representing bias. The appropriate values for weight and shift are not easy to be determined and experts' opinions, as well as sensitivity analysis, are necessary.

Use of comparative RWE as prior information: In a Bayesian framework, prior knowledge can be combined with the current data to derive the posterior distribution, representing the updated state of science on the parameters of interest (eg, treatment effects). Following this approach, the results of a Bayesian NMA including only RWE is considered as prior knowledge for the NMA of the RCTs, in a 2-step approach. The posterior of Step 1 is then adjusted for bias and used as priors for the RCT NMA. There are different approaches for the construction of the RCT NMA prior to the RWE NMA results.[6]

Three-level Bayesian hierarchical model: Three-level hierarchical models can be used to synthesize data from studies ›

with different designs (eg, RCTs, cohort studies, case–control). At the first level, each study is analyzed separately to obtain estimates of the relative effects of the interventions that are compared in the study. At the second level, studies of the same design are grouped and synthesized by means of NMA. At the third level, a NMA will synthesize the results of the design-specific NMAs to a single estimate. Furthermore, the estimates from each study (first level) or from each design (second level) can be down-weighted by inflating the variance of the estimates obtained.

Even if a properly designed RCT including the interventions, population, and subpopulations of interest is feasible, it can take years from design to completion, while in many cases relevant real-world evidence is readily available and can be used to support clinical decisions.

Beyond comparative studies: In some clinical areas, the available evidence consists mainly of single-arm studies. In this case, the family of population-adjusted indirect comparison methods has been proposed, including the matching adjusted indirect comparison and the simulated treatment comparison.[12] If patient-level data are available for the single-arm study, these can be connected to the network, following one of these methods.

BABY STEPS OUTSIDE THE COMFORT ZONE

Conducting a valid NMA with RCTs does require the use of proper methods and thorough review of the evidence base. The key is to ensure that patient and study characteristics that can act as potential treatment effect modifiers are balanced and the NMA assumptions are valid. Adding RWE is even more challenging, as it is difficult to predict the magnitude or direction of possible biases, especially when patient-level data are not available. Advancing the statistical methods, understanding the strengths and weaknesses of various data sources, and providing guidance for transparent analysis and reporting are all critical and complementary for valid NMAs, including RWE.

Despite the challenges, the wealth of RWE that is being produced at an increasing rate will become more and more difficult to be ignored or simply excluded from the decision process. The increasing granularity and complexity of RWE, together with the recent advances in data science analytics, offer opportunities to leverage these data for decision support through NMA.

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Medical Device Real-World Evidence for Beginners: A Primer

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The future of medical devices will bring with it a massive amount of data—from not only the devices themselves but also wearable and mobile technologies to which they are connected—and will present exciting new challenges and opportunities for the medical device researcher.

WHAT IS A MEDICAL DEVICE?

Medical devices include any equipment used for therapeutic or diagnostic medical purposes[1], and therefore comprise an extremely wide array of items—from tongue depressors to orthopedic implants to magnetic resonance imaging scanners and software. Medical devices used to identify the health status of a patient are considered diagnostic, while those that are valuable to treatment or amelioration of a disease or disorder are considered therapeutic.

WHAT ARE REAL-WORLD DATA (RWD) AND REAL-WORLD EVIDENCE (RWE)?

The concepts of real-world data (RWD) and real-world evidence (RWE) have evolved over the years. In 2017 guidance, the US Food and Drug Administration (FDA) articulated formal definitions: RWD are "data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources" (eg, electronic health records) and RWE is "the clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD."[2]

WHAT ARE KEY USES OF RWE FOR MEDICAL DEVICES?

Key uses of RWE for medical devices include commonplace applications such as epidemiologic and safety evaluations (eg, incidence of complications after specific device-centric surgical interventions)[3], characterizations of treatment patterns and healthcare utilization trends (eg, dissemination of new technologies such as robotics)[4], and comparative-effectiveness research (eg, comparisons of 2 or more technologies)[5]. Additionally, the FDA has recently encouraged and issued guidance on the use of RWE for regulatory purposes[2]. Such uses include support of expanded indications for use, postmarket surveillance studies, establishment of historical or concurrent control groups for nonrandomized clinical studies, and using historical data to set clinical study goals (eg, to determine equivalence of a new device to a predicate device), among others[2]. Furthermore, with the enactment of the new European Medical Device Regulation, RWE will likely play a key role in satisfying proactive surveillance requirements for medical devices marketed in Europe. In summary, RWE for medical devices can be used to provide information on a wide variety of subjects. These subjects collectively affect all stakeholders: the patients for and in whom medical devices are used, the healthcare practitioners who deliver medical device-related care, those who purchase—or influence reimbursement of—medical devices (eg, hospitals, payers), and the regulators of medical devices, among others.

FROM WHAT RWD SOURCES CAN RWE FOR MEDICAL DEVICES BE GENERATED?

Registries: Prospectively collected registries have the natural benefit of providing high-quality, detailed information on medical devices and outcomes of interest, and therefore play an extremely important role in the evaluation of medical device safety and performance. In the United States, public-private partnerships—most notably the Medical Device Epidemiology Network Initiative (MDEpiNet), through which the FDA's Center for Devices and Radiological Health (CDRH), academic and medical institutions, industry, and other governmental and private organizations have partnered—have led to the development of numerous Coordinated Registry Networks from which medical device RWE will be generated. Globally, there are also many national and international registries, with organizations such as the International Medical Device Regulators Forum (IMDRF) advocating for the use of registries for regulatory decision making.[6]

Secondary data: In some cases, the cost of collecting registry-based RWD for medical devices may be prohibitive or economically unjustified, or loss-to-follow-up rates too high for long-term quality >

and effectiveness measures (eg, 10-year hip replacement revision rates). Access to existing registry data is also generally restricted and, therefore, such data may be unavailable to a given medical device researcher. Thus, traditional secondary RWD sources are also vital to RWE generation for medical devices. Among the secondary data sources available for medical device RWE studies are: administrative payer (insurance) claims data; administrative hospital data; medical record data, including charts and electronic health records (EHRs); surveys; and expert panels.

However, identification of devices in secondary RWD sources can be challenging. Unlike pharmaceuticals, which (with some exceptions) are reimbursed directly by payers and generate a specific prescription claim with documentation of the product's National Drug Code (NCD) and other useful information for research, medical devices tend to be purchased directly by healthcare providers (hospitals and other facilities/practices, key consumers of medical device RWE) and paid under what equates to a bundled payment; reimbursement for a specific procedure will not necessarily correlate with the provider's underlying expenditure on the medical devices used therein. Although Unique Device Identifiers (UDIs)—a medical device-specific analogue to the NDC—exist, healthcare claim forms currently do not contain a field in which to record UDIs, and the documentation of standardized device identifiers is not ubiquitous in most traditional secondary RWD sources (although some healthcare systems can access UDIs from supply chain databases and link these to EHR data). Thus, medical device identification is often dependent on the device possessing a specific billing code (eg, a Healthcare Common Procedure Coding System code, which is uncommon), or mining unstructured data fields such as hospital charge master data or physician notes, which can introduce various forms of measurement error. These data sources can also lack information on important device-specific outcomes, such as device failures—which may necessitate the use of failure proxies (eg, reoperative/revisional surgery).

Table 1. Example of RWD Sources to Support RWE for Medical Devices

ADMINISTRATIVE DATABASES

Examples*:
- **Publicly Available**
  - Healthcare Cost and Utilization Project (HCUP) (eg, Nationwide Inpatient Sample)
  - Medicare/Medicaid Standard Analytic Files
  - National Hospital Discharge Survey
  - Surveillance, Epidemiology, and End Results (SEER)—Medicare
- **Payer-sourced Data**
  - Optum
  - HealthCore/Anthem, Inc
  - Blue Health Intelligence
  - Korean Health Insurance Review and Assessment
- **Hospital/Group Purchasing Organization**
  - Premier Hospital Database
  - Vizient (formerly MedAssets) Database
  - MedMining/Geisinger
  - Japanese Medical Data Vision
- **Multisource Data Consolidations**
  - IBM Watson Health/Truven/MarketScan
  - IQVIA Pharmetrics
  - Japanese Medical Data Center (Japan)
  - Orizon (Brazil)

Key Considerations:
- Relatively inexpensive and rich in data elements like diagnoses, procedures, medications, and healthcare costs/expenditures
- Typically comprise data from millions of patients and therefore are considered to have good generalizability
- Medical device identification is often dependent on the device possessing a specific billing code (eg, a Healthcare Common Procedure Coding System code), or mining unstructured data fields, such as hospital charge master data or physician notes, which can introduce measurement error
- Cannot usually answer questions such as why a provider chose one therapeutic approach over another (eg, surgery versus medication)
- Can lack information on important device-specific outcomes, such as device failures

ELECTRONIC HEALTH RECORDS

Examples*:
- Hospitals/academic medical centers
- Community practice sites
- Flatiron Health Oncology
- Cerner Health Facts
- Optum/Humedica
- US Oncology
- Practice Fusion
- GE Healthcare Centricity
- Clinical Practice Research Datalink (UK)
- IBM Watson Health Explorys

Key Considerations:
- Limited longitudinal follow-up, sometimes unable to track patients across sites of care
- Typically have same medical device identification challenges as administrative databases
- With proper design, researchers may be able to evaluate "why" events happen during treatment or treatment decision rationales
- Can lack information on important device-specific outcomes, such as device failures

SURVEYS & REGISTRIES

Examples*:
- Society of Thoracic Surgeons (STS) National Database
- Vascular Quality Initiative
- Japan PCI (Japan)
- US Cath-PCI Registry
- National Cardiovascular Data Registry's Implantable Cardiac Device Registry
- National Joint Replacement Registry (Australia)
- Kaiser Permanente National Total Joint Replacement Registry
- National Joint Registry (GB, Wales, N-IRL)
- Canadian Joint Replacement Registry
- Kaiser Permanente National Implant Registries
- European Database for Medical Devices (anticipated launch in 2020)

Key Considerations:
- Can collect and yield medical device satisfaction information directly from patients
- Provider surveys and expert panels can provide insights into clinical perspectives on drivers of treatment choice and product prescribing preferences
- Direct-to-subject study designs are often patient-centered and can capture subjective information unavailable via claims data or medical records
- Limited longitudinal follow-up; ability to link to other longitudinal data sources is inconsistent
- Information specific to the purpose of the registry design or to the remit of the expert panel is included, but they are otherwise limited in scope

** Not intended to be comprehensive; sources are US-based unless otherwise noted.*

WHAT IS THE STATUS OF RWE FOR MEDICAL DEVICES OUTSIDE OF THE UNITED STATES?

Numerous international, regional, and country-specific registries and secondary databases have been used to generate RWE for medical devices (for examples, see Table 1). Although the influence of medical device RWE varies widely by country, RWE is receiving increasingly more attention in regions such as Europe (due to the new European Medical Device Regulation) and Asia.[7] As noted above, IMDRF is one international group that is actively advocating for the use of registries for regulatory decision making related to medical devices. In 2016, the IMDRF issued a report on this subject titled, Principles of International System of Registries Linked to Other Data Sources and Tools.[6] Opportunities to be involved in RWE for medical devices outside of the United States also exist through the Observational Health Data Sciences and Informatics collaborative (https://www.ohdsi.org/), which is an open multi-stakeholder group that collectively maintains a disseminated international network of healthcare databases stored in a common data model.

WHAT KEY SOURCES OF BIAS ARE PRESENT IN MEDICAL DEVICE RESEARCH?

Studies of medical devices, particularly those that involve invasive procedures, are especially susceptible to biases. These are due to confounding by indication and difficulty in identifying appropriate comparison groups, as well as difficulties separating out the effects of a device versus the procedure.

Confounding by indication: Individuals who receive a particular device may be different from those that receive no device or a different device. In an observational study comparing outcomes of bare-metal versus drug-eluting stents, James et al found that within the first 6 months following implantation, patients who received drug-eluting stents were nearly 30% less likely to experience heart attack or death as compared to those who received bare-metal stents.[5] Most of the difference occurred in the first few days following implantation even though the benefits of preventing restenosis are not realized so quickly. Using a landmark design, in which the investigators started following patients 6 months after implantation, the cumulative risk of death or myocardial infarction was comparable between patients who received bare-metal versus drug-eluting stents, suggesting that confounding by indication biased the initial result, a limitation addressed by thoughtful design. Thus, careful control for confounding by indication is essential for RWE studies of medical devices.

As greater focus is put on RWE for medical devices, particular attention is needed to the design of real-world studies that can distinguish the effects of a device from differences in patient characteristics, medical practice, and operator.

Historical control groups: Appropriate comparator selection is perhaps the most effective strategy for addressing biases in observational studies. In a review of high-risk cardiovascular devices, Chen et al found that most studies that support device approval do not use a parallel active control group.[8] Because of the highly iterative nature of medical device development, historical control groups, comprising patients who received a different device or a different version of the device of interest, represent an attractive alternative. However, historically controlled studies require special considerations to address confounding and misclassification. For example, if medical practice and outcomes have evolved over time, there can be intractable confounding between historical and contemporary groups. Such studies are also limited to the outcomes and covariates measured in the historical cohort. Ensuring similarity in medical practice, surveillance, and measurement between periods is essential.

Provider effects: Finally, when studying medical devices, one must be clear about whether the exposure of interest is the device itself or the combination of the device plus the hospital's processes for the procedure in which the device was used and the surgical team's proficiency in conducting the procedure, as outcomes can vary based on operator experience and the process for the procedure.[9] As greater focus is put on RWE for medical devices, particular attention is needed to the design of real-world studies that can distinguish the effects of a device from differences in patient characteristics, medical practice, and operator.

WHAT IS THE FUTURE OF RWE FOR MEDICAL DEVICES?

One ongoing development in RWE for medical devices is the National Evaluation System for Health Technology (NEST), an FDA CDRH-led collaborative national evaluation system aimed at efficient and improved RWE generation for medical device evaluation and regulatory decision making. NEST will use distributed data networks to link data from clinical registries and administrative sources, with the objective to inform treatment decisions, ensure safety, and foster device innovation and patient access. NEST and its associated collaborators are currently conducting and soliciting test cases to gain insights into the practical implementation of the NEST approach to evidence generation within the medical device ecosystem.[10]

Technological innovations will also drive substantial changes. The amalgamation of advanced data analytics (eg, machine learning) and medical device engineering will create an opportunity to develop smart, intelligent, and automated devices. Mobile health apps built with data analytics could be used to automate drug delivery or simply give patients day-to-day guidance on their medical care. For example, a sensor connected to an inhaler records where, when, and why a patient takes medication, which in turn provides patients and physicians a view to better understand usage and medication adherence. Additionally, a smart medical device could collect and analyze data from disparate sources like wearables, weather reports, medical records, diagnostic results, diet-tracking apps, and more to make real-time treatment recommendations.[11,12] Medical sensors and predictive analytics could be used to circumvent adverse outcomes before they occur, for example, to help sensors learn to recognize early warning signs of serious conditions (eg, abnormal values) and trigger automatic alerts to healthcare providers.[12] >

Over the coming decade, the medical device sector is likely to see the entry of new players from other industries who can collect and analyze RWD from smart devices. Leveraging data and making investments in intelligent technology such as wearables, smart device applications, cloud-based data and analytics, and the Internet of Things will be an essential part of the new device value proposition. With the widespread dissemination of such technologies and the massive amounts of data generated from them, medical device researchers will face exciting new challenges and opportunities.

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ADDITIONAL INFORMATION

The preceeding article is based on a workshop give at ISPOR 2018.
For more on ISPOR's Medical Devices Special Interest Group, go to https://www.ispor.org/member-groups/special-interest-groups/medical-devices-and-diagnostics.

Furthering Patient Engagement in Health Economics and Outcomes Research: Exploratory Research by ISPOR and the National Health Council

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ISPOR and the National Health Council have an opportunity to leverage their organizations' strengths and member expertise to aid patient advocacy groups and help them understand how their patients and members can be best represented in health technology assessments or value frameworks.

Patient advocacy groups (PAGs) or voluntary health groups have proven to be valuable research partners in helping identify patients with certain genetic or phenotypic markers; educating patients, providers and other audiences; and aiding patients with travel to and from study sites.[1] Health economics and outcomes research (HEOR) is an area in which patient engagement is increasing.[2,3] Patient advocacy groups, as strong advocates for patients, may see value in conducting HEOR activities but may lack the expertise and/or resources to complete such a study. For example, a patient group may have existing data but lack the resources or expertise to extract meaningful and impactful insights that could meet the needs of its members.[4]

HEOR professionals may also benefit from working with patient advocacy groups. Individuals early in their careers may be able to obtain meaningful claims data or patient survey data projects or modeling experience through their interactions with patient advocacy groups. Fostering meaningful patient engagement behavior and gaining experience in this area could aid in the development of best patient-centered research practices.

The National Health Council (NHC) and ISPOR have built upon the established work of the Patient-Centered Outcomes Research Institute (PCORI) to increase the ability of patient advocacy groups to be an active participant in HEOR activities and healthcare discussions. ISPOR and NHC have an opportunity to leverage their organizations' strengths and member expertise to aid patient advocacy groups and help them understand how their patients and members can be best represented in health technology assessments or value frameworks.

Prior to ISPOR and NHC developing a mechanism to connect patient advocacy groups to HEOR professionals, more had to be learned about the characteristics, research capabilities, and unmet needs of patient advocacy groups. Patient advocacy groups vary in size, disease area of focus, and research capabilities and may be composed of individuals with a variety of backgrounds. Therefore, an environmental assessment was necessary for optimal matching between patient advocacy groups and HEOR professionals. More information was also needed from the patient advocacy group and the HEOR professional perspective to better understand how the potential partnership of 2 groups can lead to mutually beneficial outcomes. This study sought to investigate the research knowledge, perceptions, and experiences of patient advocacy groups as they relate to HEOR activities. Additionally, this study adds to the literature by providing insight to the level of engagement and interest HEOR professionals have in collaborating with patient advocacy groups on future projects.

PATIENT ADVOCACY GROUP QUALITATIVE SURVEY

A semistructured interview guide was constructed to further understand the needs of patient advocacy groups. The interview guide had the following objectives: (1) understand the HEOR needs of patient advocacy groups, (2) understand the level of knowledge of key HEOR terms, (3) explore the expectations and perceptions of HEOR, (4) identify the level of resources available to conduct HEOR, and (5) document past experiences with HEOR.

A 6-phase thematic approach to analysis was utilized:

1. Getting familiar with the data
2. Generating initial codes
3. Interpreting and sorting codes into themes
4. Reviewing themes for coherent patterns
5. Defining and naming the themes
6. Producing the report[5] >

Thirteen participants representing 11 different patient advocacy organizations, identified through the NHC network, took part in 11 separate interviews. patient advocacy groups had little to no staff specifically devoted to HEOR, and 4 interviewees stated that they were the sole person who participated in HEOR activity. Two themes were identified from the patient advocacy group interviews—increasing understanding of patients and value assessment and access to medication and healthcare.

INCREASING UNDERSTANDING OF PATIENTS AND VALUE ASSESSMENT

Several groups reported a desire to increase their knowledge of the costs incurred by patients throughout their lives. Examples of the different types of costs that patient advocacy groups sought to understand better included out-of-pocket costs, indirect medical costs, and overall societal costs of a disease. When asked to define outcomes research, patient advocacy groups tied their definition back to how a patient feels after receiving a treatment and how this impact compares to other treatment approaches the patient could have taken. Examples included symptom reduction, improvement in disease status, avoidance of hospitalizations, and economic outcomes.

with providing the patient and disease expert perspective in the development of their drug evaluations models. patient advocacy groups expressed that current value assessment tools, such as those utilized by ICER, did not entirely represent the priorities of their patient communities and that they wanted to increase the patient voice in healthcare discussions. Patient advocacy groups did not always feel that the ICER model was able to capture all areas of the disease accurately and therefore sought to shift the value assessment conversation to be more patient-centric. They wanted tools to quantify the total impact of a disease on a patient that extended beyond out-of-pocket costs and assessed their ability to work and maintain relationships with family and friends. Patient advocacy groups stated that the lack of internal resources (ie, funding, staff) limited their ability to proactively engage in value assessment and HEOR activities. Several groups reported having pieces of relevant information needed for the value discussion but lacked internal expertise to communicate the viewpoint of a patient advocacy group. Partnering with a HEOR professional was cited as an approach to fill this gap and be a stronger player in future value discussions.

The overwhelmingly positive interest level in health economics and outcomes research professionals expressing a desire to work with patient advocacy groups highlights that future partnerships are possible. The variety of volunteers from different employment sectors and varying years of experience indicate that diverse skill sets are available to meet the needs of a patient advocacy group.

All patient advocacy groups strongly believed that the definition of value depended on the perspective (ie, patient, provider, insurer) and should be extended beyond efficacy, safety, and cost. Nearly all groups sought to understand value from the patient perspective. They believed that a partnership with a HEOR professional would help them understand how to quantify value in ways that demonstrate that the patient voice is heard.

Patient advocacy groups have also been contacted by the Institute for Clinical and Economic Review (ICER) to assist

ACCESS TO MEDICATION AND HEALTHCARE

Patient advocacy groups expressed the need to demonstrate the value of treatments from the patient perspective in their conversations with payers when discussing access. Several groups believed that access to medication decisions were being made without proper representation of the patient opinion and noted that payers were making decisions about access to medications based on outcomes they viewed as not being the most clinically relevant or appropriate. Patient advocacy groups discussed partnering with physicians to write statements to combat utilization management techniques (ie, prior authorization, step therapy) used by payers or to help form their organizational positions on health policies. In addition to research, clinicians are also brought in on an ad hoc basis for several purposes, including identifying clinically significant outcomes, developing patient registries, advising on advocacy positions, or leading epidemiological studies. Healthcare access issues stemming from ensuring preventative services related to the conditions they represented remained within current insurance requirements was also another cited obstacle.

Multiple patient advocacy groups stated how such conversations reach a point where actual data are needed to support anecdotal evidence from the patient advocacy group community. Having a HEOR professional assist in conducting further analysis on patient subgroups was cited as being beneficial in patient advocacy groups having more nuanced discussions with payers. Groups also cited not having the data or information necessary when engaging with ICER throughout the review process. Increasingly, patient advocacy groups are seeing the need to have such data earlier in the drug development process to avoid barriers to access to medication shortly after regulatory approval.

HEOR PROFESSIONAL QUANTITATIVE SURVEY

An 8-item survey was developed to understand the level and type of interest and engagement HEOR professionals have in working with patient advocacy groups on a volunteer basis. The survey was created to gather information about researcher's area of expertise, employment, years of experience, previous experience working with patient advocacy groups, level of interest volunteering with a patient advocacy group, size of project they would want to be involved with, readiness to volunteer, and specific patient advocacy groups or diseases of interest.

The HEOR professional survey was sent out to a total of 4328 ISPOR members in late 2017; members surveyed included all those in an ISPOR Special Interest Group, the Student Network, or the

Faculty Adviser Council. A total of 235 participants completed the HEOR professional survey, leading to a 5.42% response rate. Respondents were most often employed within life sciences, academics, and consulting organizations. Students also made up a fifth of the participants. The majority (90.6%) of respondents reported interest in working with a patient advocacy group, with over half stating they were very interested.

As this initiative moves forward, ISPOR and NHC are seeking both HEOR scientists and patient advocacy groups who are interested in engaging in small-scale pilot projects.

Participants were open to a variety of potential patient advocacy group collaborations as all project types had over a 20% response and the majority were ready to begin work within 6 months. Oncology was the most popular disease state of interest, but most participants did not state that they had a specific interest in a patient advocacy group or disease. There was a statistically significant relationship between years of experience, as those who were earlier in their careers reported being more likely to express interest in working with a patient advocacy group ($P<0.008$).

PATIENT-RESEARCHER PARTNERSHIPS—REALIZING THE POTENTIAL

The potential for a HEOR professional and patient advocacy group partnership would allow patient advocacy groups to better understand their patients and their financial, clinical, or emotional burdens as well as value assessment methodology and HEOR. The collaboration will help patient advocacy groups circumvent their lack of internal expertise and resources and will allow them to be more well informed and generate the necessary data when having policy, advocacy, and healthcare access discussions on behalf of their patients. The overwhelmingly positive interest level among HEOR professional survey respondents in expressing a desire to work with patient advocacy groups highlights that future partnerships are possible. The variety of volunteers from different employment sectors and varying years of experience indicate that diverse skill sets are available to meet the needs of a patient advocacy group. Replicating this work among patient advocacy groups based in other countries would aid the relationship between both groups internationally. Further research on the exact patient advocacy group needs will help determine feasible projects that can be accomplished within the workload and timeframe expressed by HEOR professionals. Communication of project scope and goals of both sides is paramount prior to entering into a patient advocacy group and HEOR professional collaboration. Additional communication and vetting of the HEOR professional will allow a more accurate determination of individuals with the right balance of time, experience, and ability to successfully collaborate with a patient advocacy group.

WANT TO GET INVOLVED?

HEOR professional and patient advocacy group collaboration has the potential to be mutually beneficial for both parties. As patient engagement and the patient voice continue to be a larger part of the healthcare value discussion, collaborations between both groups can help patient advocacy groups be a more effective contributor in the assessment of health technologies. As this initiative moves forward, ISPOR and NHC are seeking both HEOR scientists and patient advocacy groups who are interested in engaging in small-scale pilot projects.

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ADDITIONAL INFORMATION

The preceding article is based on a presentation given at ISPOR 2018. To view the presentation, go to https://www.ispor.org/docs/default-source/presentations/1421.pdf?sfvrsn=8dba379c_1.

For further information, contact ISPOR at CSO@ispor.org.

Q&A

The Opioid Crisis: An Interview With Douglas C. Throckmorton, MD

Value & Outcomes Spotlight had the honor to interview Douglas C. Throckmorton, MD, the FDA's Deputy Director for Regulatory Programs in the Center for Drug Evaluation and Research. Dr. Throckmorton received his medical degree from the University of Nebraska Medical School and completed his residency and fellowship at Case Western Reserve University and Yale University, respectively. Prior to coming to the FDA in 1997, he conducted basic science research and practiced medicine at the Medical College of Georgia, Augusta, Georgia and Augusta Veterans Administration Hospital. He is a board-certified physician and as Deputy Director for Regulatory Programs, Dr. Throckmorton shares the responsibility for overseeing the regulation of research, development, manufacture and marketing of prescription, over-the-counter, and generic drugs in the United States.

Value & Outcomes Spotlight: **FDA has identified opioid addiction as the biggest public health crisis currently facing the United States. What do you view as the key measures FDA has taken to address this problem?**

Throckmorton: At FDA, we've set out to address the opioid crisis forcefully, using all the agency's tools and authorities. We've taken a range of new steps as part of a comprehensive approach, in concert with the steps that the Secretary of Health and Human Services has outlined to confront this crisis. We're leveraging our authorities to the greatest extent possible with a focus in four main areas. First, our efforts encourage more appropriate prescribing to decrease exposure to opioids and prevent new addiction and the risk of overdose; second, advancing innovation in novel pain medicines and treatments that don't have the same risks as opioids; third, the development and use of better treatments to help those with opioid use disorder; and fourth, increasing our enforcement and interdiction work aimed at illicit drugs such as fentanyl, especially when it comes to products being shipped illegally through the international mail facilities. In addition, part of our ongoing work is ensuring that drug approval and removal decisions are made within a benefit/risk framework that evaluates not only the outcomes of opioids when used as prescribed, but also the public health effects of inappropriate use of these drugs. We are continually re-evaluating the safety of approved opioid products based on both post-market data the FDA has required from sponsors and additional sources of information as part of our safety surveillance.

For members of ISPOR, a close eye is kept on the cost-effectiveness of medical and public health interventions. How is FDA evaluating the impact of its latest initiatives to combat the opioid crisis?

We are keeping a close watch on trends related to prescribing and opioid-related deaths. However, while some of the FDA's initiatives are designed to have an immediate impact, the majority may have the largest impact over time. For example, we've implemented several measures, including the Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) to help better communicate the serious risks about the use of opioid pain medications to patients and health care professionals and provide them with tools to use these powerful medicines appropriately. That REMS requires that training be made available to health care professionals to cover broader information about appropriate pain management, including alternatives to opioids for the treatment of pain. We've also awarded a contract to the National Academies of Sciences,

Engineering, and Medicine to help advance the development of evidence-based guidelines for appropriate opioid analgesic prescribing for acute pain resulting from specific conditions or procedures. These steps can help over time to reduce the rate of new addiction by decreasing unnecessary and/or inappropriate exposure to opioids and ensuring rational prescribing practices, while still providing appropriate treatment to patients who have medical need for these medicines.

Examples of those FDA initiatives aimed at having a more immediate impact include, the marked increase of our enforcement and interdiction work aimed at illicit drugs such as fentanyl, especially when it comes to products being shipped illegally through the international mail facilities. We've also been focused on criminal investigations conducted by the FDA in partnership with other federal agencies to identify suspect shipments and refer them for prosecution. Additionally, we're targeting the operations of international criminal groups, both public and on the darknet. Every package stopped, and every online network shut down and every criminal convicted reduces the risk that illegal and dangerous drugs will get into the hands of unknowing consumers. Another example is our work to spur innovation in drug development that will have an impact on opioid use and addiction. For example, if we can effectively advance new pain medicines and treatments that don't have the same risks as opioids and the development and use of better—and more accessible—treatments to help those with opioid use disorder. Just recently, we took an unprecedented step of developing a model drug facts label and conducting the necessary consumer comprehension testing to encourage drug companies to develop an over-the-counter version of the antidote to opioid overdose, naloxone, which could help save companies both time and money in developing nonprescription versions of the drug.

How did we get here? When you look at the opioid crisis, how does the blame get distributed among health system stakeholders—providers, patients, manufacturers, payers?

Many groups helped fuel this crisis. For too many years, we as doctors were too cavalier about prescribing these powerful and addictive drugs. An entire generation of physicians was trained—inappropriately we now know—on opioid prescribing practices that were far too loose. My generation of physicians fell squarely in the cohort that were trained to view pain as the fifth vital sign and to believe that the risk of addiction from opioids was very low. In the hospital, a standing order for an as-necessary prescription for Percocet was the norm.

We now know that these beliefs, and these practices, were wrong.

The FDA is also not immune from responsibility. We were too slow to act at some key moments. We were too slow to change labelling on certain drugs to discourage chronic prescribing in situations where it is inappropriate. We were too slow to recommend changing the scheduling of hydrocodone to restrict its access when there were signs of mounting abuse. And we were too slow to advance efforts to make proper physician education more routine. We need to learn from these mistakes and tragic consequences. Going forward, we need to embrace a shared commitment to correct the burdens of our collective mistakes. At the FDA, we need to make sure that our actions today are forceful enough to reverse this while in no way harming patients in need. Having allowed a crisis of historic proportions to get firmly planted, our actions today are going to have to be more forceful than the steps that might have been sufficient to address these same challenges two or five or ten years ago—if we had the foresight to intervene earlier and more aggressively as this tragedy continued to grow in depth and proportion.

Looking back, were there early warning signs of a growing crisis that policymakers were slow to act upon?

As I previously stated, the public health crisis of opioid addiction and overdose is a tragic situation that has evolved over a number of years and has been the result of a confluence of factors. Collectively we could have done better. We should have done better. And right now, we have to do better. We don't want to look back in the future again and say we didn't act quickly enough or forcefully enough to address this crisis. Importantly we know it requires an all-of-the-above approach that will require each of us to work together—the FDA and other government agencies, health care providers, the medical products industry, policy makers, patients and their families. At the FDA, we remain steadfast in using all facets of our regulatory authority to change the trajectory of this epidemic. One of the unique ways we are doing this is by using new tools to detect potential warning signs sooner and remain vigilant to recognize shifting trends in the addiction landscape. This includes recognizing patterns of prescription and illicit drug use and determining the reasons behind them using the agency's clinical, epidemiologic, basic science, and social science expertise. Taking a systematic approach to monitoring such trends should allow us to intervene promptly and appropriately and protect the public from associated risks.

The opioid epidemic is widely considered a United States problem. Is that fair or is it really a global problem?

Our focus is looking at ways within our authorities—which are limited to the U.S.—in which we can help stem the tide of the opioid crisis, which has become a public health tragedy in the U.S. and may differ across the globe. At the same time, we are aware of issues related to drug abuse worldwide, as well as approaches to treating pain, and look to other countries for lessons learned and potential best practices that we can apply to our authorities here. However, I will also say that despite much of the focus being on the U.S., there are certain global aspects that have a tremendous impact on the crisis here, such as illicit drugs like fentanyl that are being manufactured overseas and shipped to the U.S. illegally, and potentially leading to numerous fatal overdoses. Ultimately, I think it's important for everyone to be mindful of the issue regardless of where they live.

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