MAY/JUNE 2018 VOL. 4, NO. 3

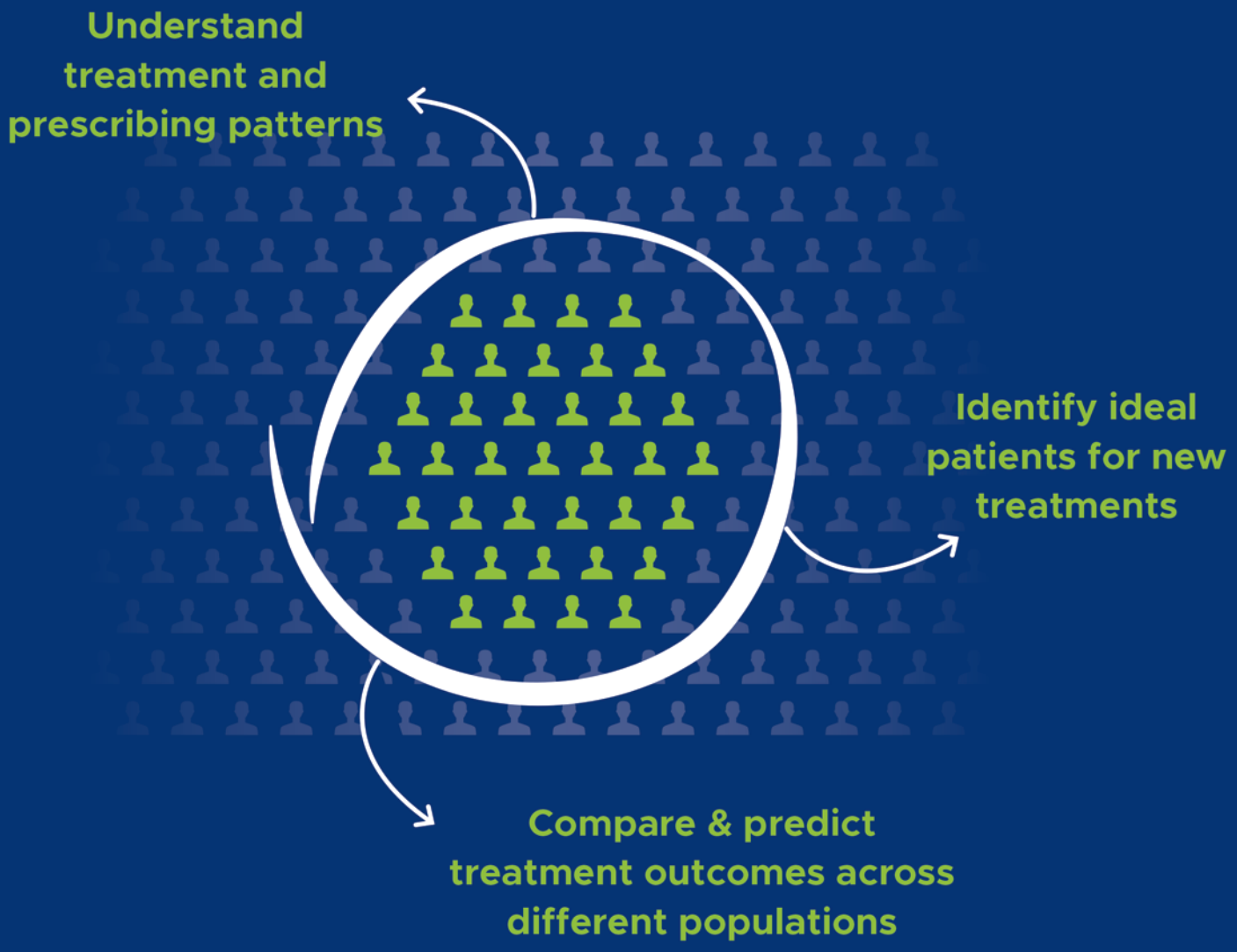
VALUE & OUTCOMES SPOTLIGHT

An ISPOR publication for the global HEOR community

The Patient's Voice in Healthcare

IN THIS ISSUE:

What if you could use curated registries to rapidly:



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VALUE & OUTCOMES
SPOTLIGHT

MAY/JUNE 2018
VOL. 4, NO. 3

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

ISPOR
Improving healthcare decisions

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FROM THE EDITOR

Recent years have given rise to patient centricity in healthcare delivery, increased role of the patient's voice in clinical research, and greater emphasis on not just patient-*reported* but patient-*relevant* outcomes in real-world evidence generation. These trends may be hitting their apex this year with many prognosticators declaring 2018 to be "The Year of the Patient."

Value & Outcomes Spotlight prides itself on keeping abreast of all things of relevance to the ISPOR community so as to keep you, the faithful reader, fully informed, so we are devoting this issue to the patient and have organized the various contributions into three categories—the patient voice, patient engagement, and rare diseases.

In the Patient Voice section, you'll find articles that address several questions (the why, when, who, where, how, what?) related to incorporating the voice of the patient in research and development, in the first article, and then in medical product life cycle management, in the second—essentially everything you need to know about incorporating the patient voice from the earliest stages of product development to the final stages of commercialization.

In the Patient Engagement section, the first article reports from the ISPOR 2017 Patient Representatives Roundtable—North America. It describes definitional and measurement issues in patient engagement, arguing that progress in understanding the value of patient engagement is being hampered by lack of clarity on the concept and lack of consensus on an evaluation structure. The second article emphasizes the importance of patient-powered research networks as a formal means of engaging patients in evidence generation, using the authors' experience in multiple sclerosis as a case example of the path forward.

The Rare Diseases section contains one article that draws attention to the particularities of eliciting the patient voice in the development of orphan drugs, proposing that mixed methods combining qualitative and quantitative approaches be utilized. A second article addresses equity issues in orphan drug pricing across the European Union.

Finally, we conclude our patient-themed issue of Spotlight with an interview with two ISPOR members who work for a company focused on drug development in the rare disease space, providing us with an insider's perspective on the challenges and rewards of bringing new interventions to those who need them most.

A lot to consider as we work our way into this Year of the Patient!

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

ISPOR SPEAKS

A Year of Transformation: ISPOR's Continued Growth and Development

Shelby D. Reed, PhD, ISPOR President

Serving as ISPOR's President has truly been an honor and a privilege. The past few months of my term have been especially productive, rewarding, and exciting. Last week, I had the opportunity to spend the day at ISPOR's headquarters in Lawrenceville, NJ, along with 2018-2019 President, Frederico Augustovski. It was energizing to meet with Nancy Berg and feel the buzz from the ISPOR staff management team working hard on behalf of members. The visit also provided a chance to walk down memory lane as I looked back at cover pages from ISPOR conferences over the past 20 years, many memories flooded back from meetings in Montreal, New Orleans, and Crystal City too. Then, a true piece of memorabilia was pulled off the shelf, a ledger (yes, *paper*!) from 1996 with names of ISPOR's (then, APOR) first members in Marilyn Dix-Smith's handwriting! I was glad that my kids were not present to see proof that their mother predated everyday use of computers! But, it was a clear reminder of just how far our organization has come. Yet, ISPOR continues to transform.

ISPOR'S TRANSFORMATION

The team at ISPOR headquarters is currently in the throes of implementing a new information technology system, website, and other staff-led projects like the new HTA Center. By this summer ispor.org will not only have a new clean professional look, but it will be totally redesigned, allowing members and others interested in HEOR information easy access to our rich knowledgebase, including our task force reports, scientific abstracts, and presentations. In addition to a polished and more functional website, the new IT infrastructure will bring better value to us as members through more streamlined processes. The last piece of the IT overhaul will provide members exciting new opportunities to network and collaborate online. Modernizing ISPOR from the inside out bolsters our Society as it is stepping into its role as the global leader in HEOR. In the sections below, I'll provide updates on a sampling of the many activities going on at ISPOR.

HEALTH SCIENCE POLICY COUNCIL

Last year, the Board of Directors approved a restructuring of the Health Science Policy Council (HSPC). The mission of the HSPC is to advise the Society on cutting-edge scientific research and research policy. The group has responsibility for overseeing Task Forces and Special Interest Groups, suggesting scientific and policy-related content, producing papers on strategic topics, and advising the Society on scientific and policy initiatives and collaborations. I recently attended the first strategic planning meeting of the restructured HSPC that was held on April 9th and 10th in Chicago. Participants included HEOR experts representing a diversity of regions and stakeholders. Discussions included longer-term goals for the current Value Frameworks and Real-World Evidence initiatives, other key topics on the horizon where ISPOR should be active, and implications for conference themes.

TOP 10 HEOR TRENDS

The HSPC was instrumental in producing ISPOR's first "Top 10 HEOR Trends" this year. The intent of this report is to help inform and spread awareness about the field of HEOR and ties in directly to ISPOR's strategic pillar of "Communication and Collaboration." If you have not yet had an opportunity to read the report, it can be downloaded at www.ispor.org/top10trends.pdf, and a complementary webinar that discussed the trends can be accessed at www.ispor.org/education/webinars/Top10Trends.html.

THE BIG EVENT—BALTIMORE, MAY 19-23, 2018

I'm thrilled that ISPOR's 2018 conference will take place in Baltimore, a city near and dear to my heart: the city where I earned my professional and graduate degrees, the city where I was married 20 years ago on a clipper ship in the Inner Harbor, and the city where I saw Cal Ripken, Jr play his 2632nd consecutive baseball game for the Baltimore Orioles. Always hoping to catch the Orioles in action, I was disappointed to learn that the team will be on the road during our meeting. On the upside, this will allow more time for the thousands of HEOR leaders from around the world to participate in 2100+ presentations. Given the enormous change in the US healthcare landscape, this year's theme, *Real-World Evidence, Digital Health, and the New Landscape for Health Decision Making*, is especially timely. Rachael Fleurence and Daniel Mullins, this year's meeting co-chairs, have put together an all-star roster of plenary speakers presenting on whether distributed research networks are ready for prime time, digital health and its potential impact on global health and health disparities, and the use of patient preference research to inform regulatory decisions. >

Carrying on with my baseball analogy, I'm excited to tell you that we have switched the lineup slightly this year with the addition of a special afternoon keynote session on Monday afternoon (May 21st) by Harlan Krumholtz, MD, from Yale University's School of Medicine. I'm certain that Harlan will hit it out of the park.

> Modernizing ISPOR from the inside out bolsters our Society as it is stepping into its role as the global leader in HEOR.

WOMEN IN HEALTH ECONOMICS AND OUTCOMES RESEARCH INITIATIVE

Of special interest to me is the recently launched "Women in Health Economics and Outcomes Research" initiative. ISPOR debuted this initiative last November at ISPOR Europe 2017 in Glasgow, Scotland, UK. The vision of ISPOR's new "Women in HEOR" initiative is to support the growth, development, and contribution of women in HEOR; to serve as a catalyst for women's leadership in the field, and to offer a platform for ISPOR women to collaborate, network, share, and mentor each other. Please join us at the upcoming "Women in HEOR" session scheduled at ISPOR 2018 in Baltimore, MD, USA. This session will be held Monday, May 21 from 12:30 PM to 2:00 PM and feature a special guest speaker, Laurie Cooke, CEO of the Healthcare Businesswomen's Association.

ISPOR'S VISION FOR THE FUTURE

ISPOR's current strategic plan approved by the Board in 2016 has served the Society well. The Board and staff review the plan annually and develop operating plans based on ISPOR's vision, mission, strategic pillars, and goals. It is now time to review and refresh the strategic plan and establish new priorities for the future. I am delighted that Bill Crown, past ISPOR President and past Chair of the Strategic Planning Working Group in 2015, has agreed to direct a group of HEOR thought leaders to chart the future path for ISPOR and for the science of HEOR. I look forward to being part of this new working group in my role as Past-President with our new President Federico Augustovski.

It's hard to believe that my year as President is coming to a close. I want to sincerely thank the members of the ISPOR 2017-2018 Board of Directors for their hard-work, dedication, and inspiration. And, I look forward to seeing many of you in Baltimore!

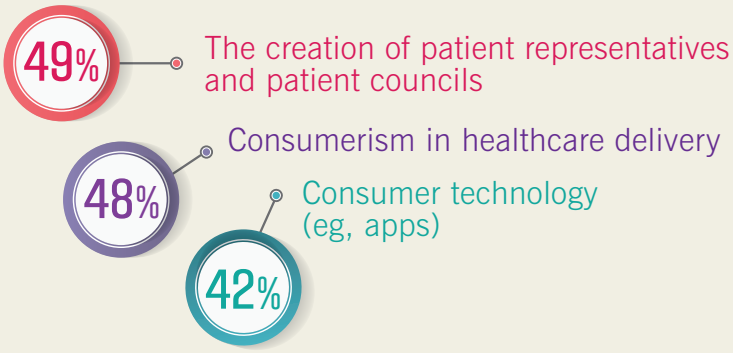
By the Numbers

Section Editor: The ISPOR Student Network*

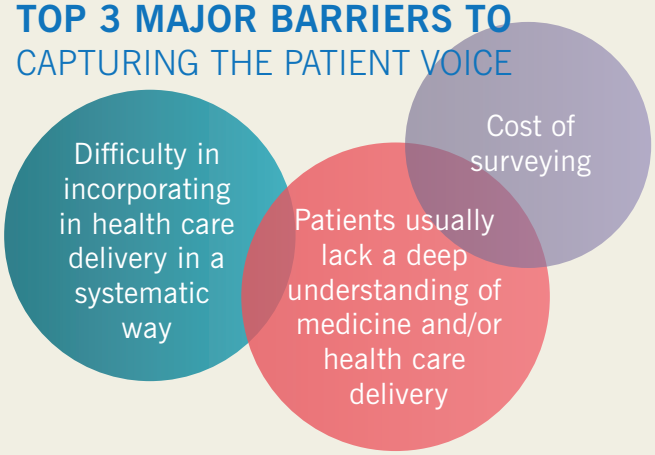
THE PATIENT'S VOICE IN HEALTH CARE

Highlights from Student Research

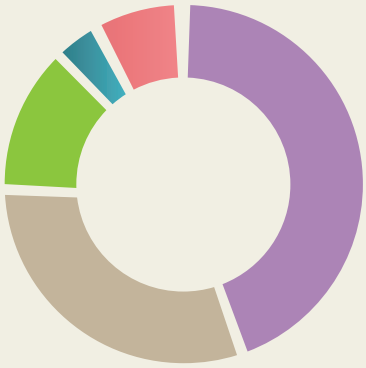
TOP 3 PROMISING TRENDS FOR CAPTURING THE PATIENT VOICE



TOP 3 MAJOR BARRIERS TO CAPTURING THE PATIENT VOICE

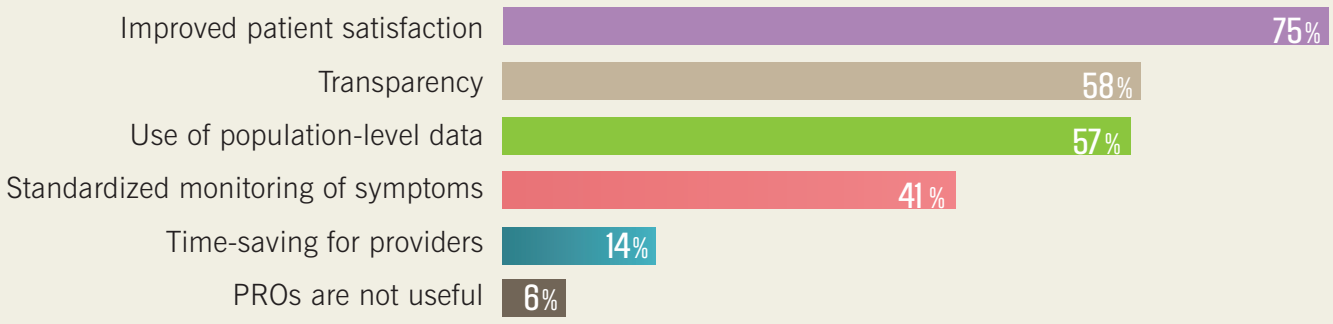


THE MOST IMPORTANT REASON HEALTHCARE ORGANIZATIONS GATHER PATIENT INPUT AND FEEDBACK



- 45% To improve delivery of healthcare
- 30% To improve quality outcomes
- 14% As a means of treating patients as customers
- 8% Other
- 4% To reduce cost

THE MOST IMPORTANT USES OF PATIENT-REPORTED OUTCOMES



Source: https://catalyst.nejm.org/measuring-matters-capturing-patient-voice/

Contributors: Claire Gorry, Trinity College Dublin, Ireland; Azfar Akram, University of Balochistan, Pakistan; Faiza Fayyaz, University of Balochistan, Pakistan Jayesh Patel, West Virginia University, USA; Blythe Adamson, University of Washington, USA; Judith John, National College of Pharmacy, Kerala, India; Zoe Szewczyk, University of Newcastle, Australia

HEOR NEWS

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

1 Too High or Too Low? ESMO's Clinical Benefit Scale Fuels Debate Over Approval Thresholds (Cancerworld)

Should regulators insist on robust evidence that a new drug shows clear benefit to patients as a condition of approval, or are demands for such levels of certainty unrealistic, or even unethical? Marc Beishon reports on how ESMO's new scale for scoring clinical benefit has added a new dimension to this long-running debate.

http://cancerworld.net/cover-story/too-high-or-too-low-esmos-clinical-benefit-scale-fuels-debate-over-approval-thresholds/

2 More Health for the Money: How to Make Universal Health Coverage a Reality for Everyone, Everywhere (Center for Global Development)

Each year, millions of people fall into poverty because they have to pay out of pocket for medical care. At least half of the world's population does not have access to essential health services. Universal health coverage is the goal of ensuring that everyone, everywhere can access quality health services without the risk of financial hardship. We can make universal health coverage happen in our lifetime by targeting investments and incentives on the highest impact interventions among the most affected populations in developing countries.

https://www.cgdev.org/blog/more-health-money-how-make-uhc-reality-everyone-everywhere#.WsZDYm4PpXo.twitter

3 Surgeon General Urges More in US to Carry Naloxone; Drugmakers Address Cost (S&P Global)

In the latest measure to help curb the opioid epidemic, US Surgeon General Jerome Adams issued a public health advisory calling for more Americans to carry the rapid-acting overdose-reversing agent naloxone, an action he said could prevent more deaths from the misuse of prescribed medicines like fentanyl or illicit drugs like heroin.

https://platform.mi.spglobal.com/web/client?auth=inherit#news/article?id=44142833&cdid=A-44142833-13613

4 JPM, Amazon, Berkshire Will Use Data to Improve Healthcare (Reuters)

JPMorgan Chase & Co, Amazon.com Inc, and Berkshire Hathaway will focus on the biggest health issues threatening the US economy in their new joint venture, including aligning healthcare payments with employee health and addressing chronic diseases, CEO Jamie Dimon said in his annual letter to shareholders.

https://www.reuters.com/article/us-jpmorgan-dimon-letter-healthcare/jpm-amazon-berkshire-will-use-data-to-improve-healthcare-idUSKCN1HC2C7

5 Taxes for Health: Evidence Clears the Air (The Lancet)

Non-communicable diseases are the leading cause of premature death in most of the world, and lower income households in most societies bear a disproportionate share of the associated preventable deaths. The papers by the Lancet Taskforce on non-communicable diseases and economics are a welcome addition to the evidence we need for reducing this disease burden. The papers show yet again that the necessary prevention and control measures for non-communicable diseases are multisectoral. The Lancet Taskforce on non-communicable diseases and economics highlights the role of fiscal policies in encouraging healthy diets and lifestyles to reduce the largest contributors to preventable non-communicable diseases—namely, smoking, harmful alcohol consumption, and obesity.

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30629-9/fulltext?utm_campaign=tlwncdsecon18&utm_content=69633114&utm_medium=social&utm_source=twitter

6 Precision Medicine, Genome Sequencing, and Improved Population Health (JAMA)

Despite controversy, major health systems across the globe are obtaining and making use of genome sequence data in patients they care for, hoping this approach will prove beneficial. Genome sequencing technology, a key driver of precision medicine, has improved substantially in accuracy, speed, and cost. As a consequence, clinicians, health systems, and governments acknowledge that individuals can have their genome sequenced and interpreted for about the cost of commonly used advanced diagnostic imaging tests. This makes obtaining genome sequence data for large numbers of individuals with and without known health issues possible.

https://jamanetwork.com/journals/jama/fullarticle/2675723

7 A Billionaire Couple Is Pumping Money into the Drug Pricing Debate. Can They Loosen Pharma's Grip? (STAT News)

John Arnold is legendary for turning contrarian bets into heaps of money. The soft-spoken Texan was a whiz kid trader at Enron before its fall. He then ran his own hedge fund, specializing in energy trading. Before he turned 34, he was a billionaire. He can afford his prescription drugs. But Arnold, now a philanthropist with a technocratic bent, has been investing considerable money lately into projects aimed at lowering or rethinking drug prices—a populist cause more often associated with activists and patients than a rich guy who made his name in finance.

https://www.statnews.com/2018/03/26/john-laura-arnold-drug-prices/?utm_content=buffer0aee0&utm_medium=social&utm_source=twitter&utm_campaign=twitter_organic

HEOR NEWS

8 Amgen's Money-Back Guarantee for Its Pricey Cholesterol Drug May Not Deliver (Pharmalot)

Over the past couple of years, drug makers have increasingly explored outcomes-based contracting as a way to convince payers to cover their medicines. Basically, this notion revolves around the idea that an insurer will get a drug at a lower cost if a patient does not benefit as planned. But not all deals are likely to deliver, and a new analysis argued that an agreement offered by Amgen is a notable example.

https://www.statnews.com/pharmalot/2018/04/02/amgen-money-back-guarantee-cholesterol-price

9 Promise and Reality of Price Transparency (NEJM)

Patients face increasing out-of-pocket healthcare costs and can save money by seeking care from lower-priced providers. Accurate, accessible price information is needed. The authors discuss the limited success of price-transparency initiatives in reducing healthcare spending.

http://www.nejm.org/doi/full/10.1056/NEJMhpr1715229?query=featured_home

10 How Much Is Too Much? What Does the US Actually Spend on Healthcare Administration? (The Incidental Economist)

The United States spends much more on healthcare each year than wealthy equals around the globe. That's not just true for spending on direct patient care, but also for spending on healthcare administration. Many scholars recognize the cost containment potential in curbing administrative costs. Determining just how much the US spends on healthcare administration and in what ways are critical first steps.

https://theincidentaleconomist.com/wordpress/how-much-is-too-much-what-does-the-us-actually-spend-on-health-care-administration/

RESEARCH ROUNDUP

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

Engagement of Canadian patients with rare diseases and their families in the lifecycle of therapy: A qualitative study

Young A, Menon D, Street J, Al-Hertani W, Stafinski T.
Patient. Published online: January 2018.

In this Canadian study, the researchers aimed to explore ways in which patients with rare disease and their families would like to be involved in the lifecycle of therapies and identify their priorities in this involvement.

Patients and their families identified opportunities that were classified into 3 objectives:

1. Incorporation of their "lived experience" into the coverage decision making (ie, new therapies funding decisions)
2. Better care for patients with rare diseases
3. Increased awareness of rare diseases.

For researchers interested in HEOR, these results can be inspiring and help apply this same process in other populations. Generating information about what the patient really wants and how he/she wants to participate in the processes will be extremely helpful, as cultural issues, access to healthcare, and the proper organization of health systems differ from one jurisdiction to the other.

Decision making in NICE single technological appraisals: How does NICE incorporate patient perspectives?

Hashem F, Calnan MW, Brown PR.
Health Expect. 2018;21(1):128-137.

In light of an explicit mandate to include patient and public involvement in the appraisal of medicines, NICE is using an appraisal committee to help make decisions on whether to fund a drug. This article describes how NICE single technological appraisal committees attempt to incorporate the patients voice in NHS funding decisions.

The relevance and importance of patients' perspectives were recognized by the committee members, who generally expressed that these views were central to enable a complete appraisal of the drug technology under assessment.

The study has shown that patient experts have provided a symbolic and representative function at committee meetings where the patient voice is discussed.

The authors conclude that, despite the establishment of a public commitment to incorporate the patient perspective and voice, the systematics to involve users marginalizes the patients and other groups of interest that sought inclusion in the STA evaluation meetings.

From a HEOR perspective these results may be a wake-up call for the need for further discussion on the topic, since patient-reported outcomes may not be fully considered in healthcare decision making.

Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: The SPIRIT-PRO extension

Calvert M, Kyte D, Mercieca-Bebber R, et al.
JAMA. 2018;319(5):483-494.

The SPIRIT-PRO guidelines provide recommendations for items that should be addressed and included in clinical trial protocols in which patient-reported outcomes (PROs) are a primary or key secondary outcome. Improved design of clinical trials including PROs could help ensure high-quality data that may inform patient-centered care.

This SPIRIT 2013 and the SPIRIT-PRO extension checklist identifies 33 items to address in a clinical trial protocol to achieve the inclusion of patient-reported outcomes in clinical trial protocols.

Should this checklist become widely used in the development of clinical trial designs, this article may have an impact on HEOR studies since new outcomes can be studied and used to evaluate a new health technology from the patient's voice consideration.

Note: The preceding texts are simplified summaries of the published articles. They do not contain an opinion or an in-depth analysis on the results obtained by the authors. The selection of these works was made based on theme relevance, not a product of a literature review or of a methodological quality selection.

CONFERENCES & EDUCATION

ISPOR Asia Pacific 2018

The leading Asia Pacific conference for health economics and outcomes research

8-11 September 2018

Keio Plaza / Tokyo, Japan

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

The ISPOR Asia Pacific 2018 Conference features invited HEOR expert speakers, 3 thought-provoking plenary sessions, and 18 Short Courses (including 5 new Short Courses) focusing on timely and important issues facing healthcare systems across Asia Pacific. In addition to the robust scientific program, there will be ample networking opportunities including a Welcome Reception that will showcase breathtaking and interactive cultural performances of Japan.

Full program, including 2 Special Sessions, will be announced in May!

Expanded Poster Sessions due to high demand!

Plenary topics:

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

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

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

5 NEW Short Courses:

– Budget Impact Analysis I: A 6-Step Approach
– Medical Devices in Asia Pacific: Regulatory and Reimbursement Issues
– Budget Impact Analysis II: Applications and Design Issues
– Applied Modeling
– Introduction to Big Data Analysis: Graph Analytics

Current program is now available on the ISPOR Asia Pacific 2018 website at www.ispor.org.

Anticipated: 1500 attendees • 950+ presentations • 25 exhibitors • 28 supporting institutions

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

Early registration deadline: 17 July 2018

#ISPORTokyo

ISPOR Dubai 2018

19-20 September 2018
United Arab Emirates

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

Featured Topics of Discussion:

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

- ***Role of HEOR In Decision Making: Global Knowledge for Local Application***
- ***Improving Access to Innovative Health Technologies***
- ***Pricing and Reimbursement: Issues and Challenges***
- ***HTA Implementation Roadmap in the Middle East and North Africa***

1st Educational Seminar: ***Introduction to Health Economics***

The session will introduce health economics as a sub-discipline of economics and its relevance to decision making in the healthcare sector.

Speaker: **Nancy J. Devlin**, BA Hons, PhD

2nd Educational Seminar: ***Introduction to Health Technology Assessment***

This session will introduce health technology assessment (HTA), the context of how it fits into healthcare decision-making, and its relevance to evidence-based health policy and the implementation of efficient healthcare.

Speakers: **Zoltan Kalo**, PhD; **Panos Kanavos**; **Finn B. Kristensen**, MD, PhD

Meeting components: health economics and health technology assessment seminars • educational symposia • ISPOR Arabic Network Meeting and HTA Roundtable – MEA (by invitation only) • welcome reception and networking opportunities

Register by 7 August 2018 and SAVE!

#ISPORDubai

CONFERENCES & EDUCATION

Summit 2018

October 19, 2018
Washington, DC, USA

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

ISPOR Europe 2018

10-14 November 2018
Barcelona, Spain

Anticipated: 5000 attendees • 2400 presentations • 100 exhibitors • 15 sponsors

Available now: call for abstracts • exhibitor and sponsor opportunities

Abstract Submission Deadline: 13 June 2018 *Help shape the content of this conference by submitting your research abstract, issue panel proposal, or workshop proposal to present in Barcelona!*

Early Registration Deadline: 25 September 2018

Deadline: 22 August 2018

Reserve your hotel accommodations now.

Visit www.ispor.org for details.

#ISPORBarcelona

Educational Trainings:

ISPOR Health Technology Assessment - USA Training Program
June 19-21, 2018 | Princeton, NJ, USA

ISPOR Health Technology Assessment Training Program
23-26 July 2018 | Lima, Peru

ISPOR ESSENTIAL HEOR EDUCATION

ISPOR Tokyo 2018: *The* HEOR Conference in Asia-Pacific

Takashi Fukuda, PhD, National Institute of Public Health, Saitama, Japan; **Shinya Saito, MD, PhD**, Okayama University, Tokyo, Japan

It is our great pleasure to invite you to Tokyo for the ISPOR Asia-Pacific Conference on 8-11 September 2018. As the leading health economics and outcomes research (HEOR) conference in the region, ISPOR Asia Pacific 2018 will address some important issues facing healthcare for populations living in this geographic region. Healthcare in Asia Pacific is undergoing a massive paradigm shift as countries find the new ways to harness HEOR to control rising healthcare costs while improving efficiency, quality, and patient access to health technologies. A few examples of this include: (1) Japan's pilot health technology assessment (HTA) program to provide evidence for the future repricing of drugs and medical devices; (2) China's HTA being included into the national health legislation and its HTA institutionalization and application; and (3) Korea and Australia's ongoing exploration of new methods, such as risk-sharing arrangements and real-world evidence (RWE) to deliver better value to healthcare.

The conference theme, "Moving Into Action: Informing Policy and Strengthening Healthcare Systems in Asia Pacific," features invited HEOR expert speakers and 3 thought-provoking plenary sessions focusing on timely and important issues facing healthcare systems across Asia Pacific. The first plenary, "Transforming Healthcare and Leveraging Digital Health for Better Health in Asia Pacific," explores the current challenges and possibilities in digital health in Asia Pacific, with important insight about how to grasp benefits and potential from those furthest in their digital journey. The second plenary, "Real-World Evidence in Asia Pacific: Are We Ready? Is It Helpful for Decision Makers?" discusses the reality of RWE and its potential value, examines readiness of RWE in healthcare decision making in the region, and explores how we should approach RWE to get the most out of it. Speakers from various sectors will share their perspectives and experiences. The third plenary, "Risk-Sharing Agreements: Country Experiences, Challenges, and Lessons Learned," will discuss the use of risk-sharing agreements to manage costs, mitigate risk, and improve patient access to innovative therapies. Key issues and practical challenges in implementing risk-sharing agreements will be addressed.

In addition to the plenaries, the program also includes a short course program with 18 courses (5 new courses for Tokyo), issue panels, workshops, research presentations, as well as an eye-catching welcome reception celebrating Japanese culture and numerous invaluable networking opportunities with global colleagues. There will also be a special session on Japan's pilot HTA program.

We also welcome you to explore Tokyo, a vibrant and culturally rich city, which offers breathtaking sights and unique cuisine. You can indulge in the exquisite cuisine of Japan at Tsukiji Market, enjoy shopping in the colorful Shibuya, Shinjuku, and Ginza districts, explore traditional Japanese culture at the Asakusa district, and maybe even take a car ride to the iconic Mt. Fuji.

We look forward to welcoming you in Tokyo this September to celebrate another landmark conference for ISPOR in Asia Pacific!

FROM THE JOURNALS

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

For more information, visit: www.ispor.org/valuehealth_index.asp.

May 2018

THEMED SECTION: Rare Diseases

The May 2018 issue features a themed section on rare diseases, edited by Kati Copley-Merriman. This themed section included 9 papers, plus an editorial, and discusses a number of issues on rare diseases relating to patient access.

Editorial

Rare Diseases: Addressing the Challenges in Diagnosis, Drug Approval, and Patient Access

Kati Copley-Merriman

Articles

Challenges in Research and Health Technology Assessment of Rare Disease Technologies: Report of the ISPOR Rare Disease Special Interest Group

Sandra Nestler-Parr, Daria Korchagina, Mondher Toumi, Chris L. Pashos, Christopher Blanchette, Elizabeth Molsen-David, Thomas Morel, Steven Simoens, Zoltán Kaló, Ruediger Gatermann, Ken Redekop

The Problem of Rarity: Estimation of Prevalence in Rare Disease

Stéphane Auvin, John Irwin, Paul Abi-Aad, Alysia Battersby

Clinical Outcome Assessments: Use of Normative Data in a Pediatric Rare Disease

Dawn Phillips, Beth Leiro

Economic Modelling Considerations for Rare Diseases

Christopher Knight, Isobel Pearson, Ben Rothwell, Andrew Olaye

Budgetary Impact and Cost Drivers of Drugs for Rare and Ultra-Rare Diseases

Michael Schlander, Charalabos-Markos Dintsios, Afschin Gandjour

Can Severity Outweigh Smaller Numbers? A Deliberative Perspective from Canada Monica Magalhaes

Societal Preferences for Funding Orphan Drugs in the United Kingdom: An Application of Person Trade-Off and Discrete Choice Experiment Methods

Dyfrig Hughes, Siobhan Bourke, Catrin Plumpton

Evaluating and Valuing Drugs for Rare Conditions: No Easy Answers

Dan Ollendorf, Richard Chapman, Steven D. Pearson

Patient Access to Medicines for Rare Diseases in European Countries

Mitja Kos, Andreja Deticek, Igor Locatelli

June 2018

COMPARATIVE EFFECTIVENESS RESEARCH/HEALTH TECHNOLOGY ASSESSMENT

Selection of and Evidentiary Considerations for Wearable Devices and Their Measurements for Use in Regulatory Decision Making: Recommendations from the ePRO Consortium

Bill Byrom, Chris Watson, Helen Doll, Stephen Joel Coons, Sonya Eremenco, Rachel Ballinger, Marie Mc Carthy, Mabel Crescioni, Paul O'Donohoe and Cindy Howry on behalf of the ePRO Consortium.

Wearable devices offer huge potential to collect rich sources of data to provide insights into the effects of treatment interventions. However, limited regulatory guidance on the use of wearables in clinical trial programs has been published. The objective of this report is to present recommendations regarding the selection and evaluation of wearable devices and their measurements for use in regulatory trials and to support labeling claims.

ECONOMIC EVALUATION

A Transparent and Consistent Approach to Assess US Outpatient Drug Costs for Use in Cost-Effectiveness Analyses

Joseph F. Levy, Marjorie A. Rosenberg, David J. Vanness

The authors of this paper review available cost measures and propose a novel strategy that is transparent, consistent and applicable to all CEAs taking a US healthcare sector or societal payer's perspective.

METHODOLOGY

Experiences of Structured Elicitation for Model-Based Cost-Effectiveness Analyses

Marta A Soares, Linda Sharples, Alec Morton, Karl Claxton, Laura Bojke

The authors of this paper review applications of SEE in cost-effectiveness modelling with the aim of summarizing the basis for methodological choices made in each application and record the difficulties and challenges reported in the design, conduct and analyses.

Value in Health

Call for Papers

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

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

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

The Editors are soliciting proposals for papers on any topic, no matter how unconventional. This is the time to be creative.

Potential topics might include, but not restricted to:

- How has the definition of value in healthcare changed over the past two decades?
- How have regulatory agencies' views evolved regarding their role in determining value in healthcare?
- If QALYs have inadequacies, what would an alternative measure of benefit look like?
- The exponential growth in cost-effectiveness analyses suggests that their importance and impact has matured, but is there empirical evidence for that?
- If Markov models are the norm, how would we decide that we need alternative modeling approaches?
- Has the increased complexity of health economic models advanced the field by improving scientific validity or further confused decision makers?

Authors should submit manuscripts through our web-based tracking system at https://mc.manuscriptcentral.com/valueinhealth and indicate in the cover letter that it is part of the "Back to the Future" themed section.

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ISPOR
Improving healthcare decisions

THE PATIENT VOICE

The Why, Where, Who, How, and What of the Patient Voice in R&D

Lars Joensson, Grünenthal, Aachen, Germany

KEY POINTS

The patient perspective can be particularly relevant in rare diseases where there is limited research available, or in therapeutic areas where there is a lack of objective outcome measures, such as a scan or a blood test.

Patients can provide information about what the disease means for them so that new tools and interventions can be developed that will make a meaningful difference to their daily lives and be more likely to show clinical efficacy.

Patients can provide valuable insight across all stages of drug development—from the initial discovery phases, all the way through to launch and post-approval activities.

WHY IS IT IMPORTANT TO INCLUDE THE PATIENT VOICE IN R&D?

Pharmaceutical companies are responsible for developing life-changing products that meet the needs of patients, clinicians, and payers. Traditionally, patients have taken a backseat in the drug development process and other stakeholders have taken priority [1,2]. Patients often have been involved only during late-stage clinical trials where they have been expected to comply with a treatment regimen that targets symptoms that may not be the most relevant to them or has side effects that affect tolerability [2].

The digital age in which we live in means that patients are now taking more of an interest as they have greater access to information about their health. Regulators are also recognizing this shift and both the EMA and FDA have published guidance documents on how the industry should drive patient-focused drug development [3,4].

Pharmaceutical companies are beginning to recognize that patients should be equal stakeholders in all stages of research and development. The patient perspective can be particularly relevant in rare diseases where there is limited research available, or in therapeutic areas where there is a lack of objective outcome measures, such as a scan or a blood test. One good example of this is chronic pain. How pain is perceived and described differs depending on a person's culture and nationality. Existing tools used to measure pain do not capture this accurately, and this presents a real problem when they are being used to test the efficacy of a new therapy in clinical trials. This is where listening and learning from patients can really help. Patients can provide information about what the disease means for them so that new tools and interventions can be developed that will make a meaningful difference to their daily lives and be more likely to show clinical efficacy.

WHERE IN THE R&D PROCESS SHOULD THE PATIENT VOICE BE INTEGRATED?

Patients can provide valuable insight across all stages of drug development—from the initial discovery phases, all the way through to launch and post-approval activities (Figure 1). In particular, patients can contribute to disease understanding and input into clinical trial design.

These insights may not otherwise be available as expert clinicians only treat a small number of patients, particularly in >

Figure 1: Where the patient voice can be integrated into R&D.

Table 1: The different levels of patient engagement.

Patient engagement can occur at several levels:

Individual patients	Persons with the personal experience of living with a disease who can contribute using their disease and treatment experience
Carers	Persons supporting individual patients such as family members as well as paid or volunteer helpers
Patient advocates	Persons who have the insight and experience in supporting and providing a public voice for a larger population of patients living with a specific disease — they may or may not be affiliated with an organization
Patient organization representatives	Persons with a high level of expertise and who represent and express the collective views of a patient organization on a specific issue or disease area
Patient experts	Persons with disease-specific expertise and who have technical knowledge in R&D and/or regulatory affairs through training or experience

https://www.eupati.eu/patient-involvement/guidance-for-patient-involvement-in-industry-led-medicines-rd/#Defining_patient *Adapted from: EUPATI*

rare diseases. Patient organizations, on the other hand, have close contact with members (often several thousand) and therefore have the required expertise and wealth of experience to help establish the priorities for patients with a particular disease.

WHO DO YOU ENGAGE WITH?

Working with the right patient experts can have a huge impact on the effectiveness of patient engagement and ultimately the development of meaningful treatments. Patient experts can be identified through existing relationships with healthcare professionals (HCPs) or trial sites, patient advocacy groups, or via online mapping of social media channels.

HOW CAN YOU ENGAGE PATIENTS IN R&D?

There are many ways to integrate the patient voice into R&D, from working with individual patients to hundreds of patients via collaboration with multiple advocacy groups (Table 2). The approach should be altered depending on the stage in the drug development process and the question that needs to be answered.

Table 2: The different approaches to patient engagement in R&D.

1:1 interviews	Similar to clinical KOLs, patient advisors are external consultants whose main role is to contribute, as required, with their subjective disease and treatment experience.
Focus groups	Interviews can be performed with individual patients and be used to collect in-depth information on the views, experiences and beliefs of individuals on a particular topic.
Advisory boards	Focus groups typically consist of 4 to 6 non-expert attendees where the intent is to obtain opinions on a specific product/topic in a group setting rather than individual responses.
Surveys and questionnaires	Advisory boards typically consist of 6 to 8 experts offering advice and perspectives on a specific topic. "Experts may be healthcare professionals or patients.

WHAT HAPPENS NEXT?

The empowerment of patients and the inclusion of their voice into the drug development process will undoubtedly continue to shift the healthcare landscape. Improvements in technology will also make a large impact as it brings the opportunity for patients to manage their health using smartphone apps and wearable devices that send medication reminders and collect real-time data that can monitor and prevent health issues. Over the coming years it will be interesting to watch the evolution in the industry as it has the potential to unlock new, more relevant treatments that improve the lives of patients.

REFERENCES

1. Improving R&D Success Through Patient Engagement & Involvement. Available at: https://www.kasocio.com/improving-rd-success-through-patient-engagement-involvement/. Accessed March 23, 2018.

2. Why Pharma Needs A New Approach To Patient Engagement In Drug Development. Available at: https://www.clinicalleader.com/doc/why-pharma-needs-a-new-approach-to-patient-engagement-in-drug-development-0001. Accessed March 23, 2018.

3. EMA. The patient's voice in the evaluation of medicines. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/10/WC500153276.pdf. Accessed March 23, 2018.

4. FDA. Plan for issuance of patient-focused drug development guidance. Available at: https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM563618.pdf. Accessed March 23, 2018.

THE PATIENT VOICE

Giving Patients' Preferences a Voice in the Medical Product Life Cycle: Why, When, and How? The public-private PREFER project: Work package 2

Esther W. de Bekker-Grob, Erasmus Choice Modelling Centre, Erasmus University Rotterdam, The Netherlands; **Juhaeri Juhaeri**, Sanofi, Bridgewater, NJ, USA; **Ulrik Kihlbom**, Uppsala University, Sweden; and **Bennett Levitan**, Janssen R&D LLC, Titusville, NJ, USA, on behalf of the PREFER consortium

KEY POINTS

The PREFER project has been launched recently to address the lack of standards and regulatory requirements for when and how to consider patients' preferences in the medical product life cycle (MPLC).

Work Package 2 (WP2) is the first step of PREFER and aims to answer the main research question: "When and how to consider patients' preferences in the MPLC".

The eight tasks of WP2 will serve as an important starting point to develop a systematic approach for considering the use of patient preferences across the MPLC.

Medical products are developed for patients. Taking the patient perspective into consideration and the need to provide more avenues for patient engagement have become increasingly important for not only the companies that develop new medical products, but also for the authorities that assess, regulate, and decide which medical products are effective, safe, well tolerated, and cost-effective [1-4]. One of the most important components of the patient perspective are patient preferences, qualitative or quantitative assessments of the relative desirability or acceptability to patients of treatment alternatives or the benefits, harms, and other properties that differ among health interventions [5]. As such, there is an emerging consensus among industry, regulatory authorities, academia, health technology assessment (HTA) bodies, reimbursement agencies, clinicians, and patient organizations that patients' preferences should be taken into account in the medical product life cycle (MPLC) [6].

Currently, however, the lack of standards and regulatory requirements for when and how to consider patients' preferences in the MPLC hampers patients' preferences taking a key position in MPLC decisions. More specifically, there is currently limited understanding or agreement of (1) the key needs and concerns that relevant stakeholders (industry, regulatory authorities, HTA bodies, reimbursement agencies, clinicians, and patient organizations) have on the collection and use of patient preferences in the MPLC; and (2) which patient preference methods are most promising to inform benefit-risk decision making for industry, regulatory authorities, HTA bodies, and reimbursement agencies at different decision points in the MPLC [5, 7]. The PREFER project—a public-private research initiative—has been launched recently to address these and related research questions.

PREFER is a 5-year project funded equally by the Innovative Medicines Initiative (IMI; Europe's largest public-private initiative aiming to speed the development of better and safer medicines for patients) and by industry as an in-kind contribution. IMI is a partnership between the European Union's Horizon 2020 program and the European pharmaceutical industry represented by EFPIA (the European Federation of Pharmaceutical Industries and Associations) (see de Bekker-Grob et al. [6] for more details). The results of PREFER will be disseminated broadly, including at the annual international and European ISPOR meetings, its Health Preference special interest group, and articles in *Value in Health*.

PREFER WORK PACKAGES AND THEIR SIGNIFICANCE

PREFER contains four work packages, including a management work package (WP1) (Figure 1). Work package 2 (WP2) is the starting point of PREFER and aims to answer the main research question: "When and how to consider patients' preferences in the MPLC." To provide more trust and evidence, PREFER work package 3 (WP3) will empirically test the findings and detected research questions from WP2 in different clinical case studies. Finally, to develop guidelines for the design, conduct, analysis, and reporting of patient-preference studies, work package 4 (WP4) will generate recommendations on patient-preference elicitation to inform decision making during the MPLC using the >

> ...the lack of standards and regulatory requirements for when and how to consider patients' preferences in the MPLC hampers patients' preferences taking a key position in MPLC decisions.

Figure 1: PREFER Work Packages (WP) focus on when and how to consider patients' preferences in the medical product life cycle (MPLC).

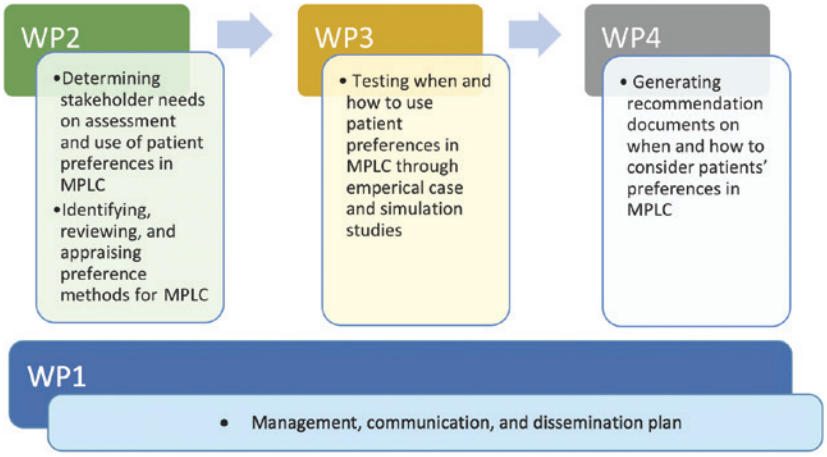
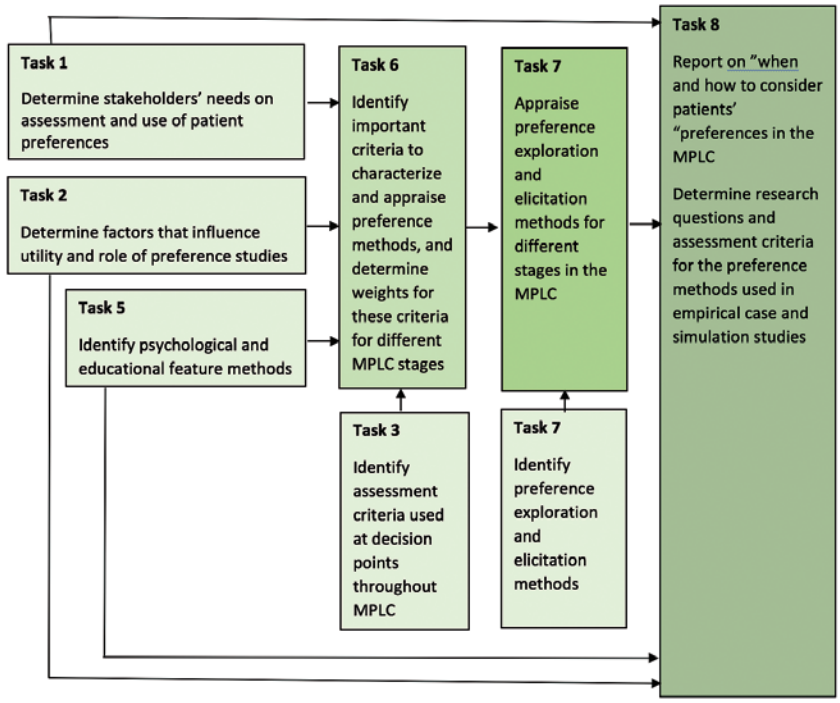


Figure 2: Conceptual model of PREFER Work Package #2 (WP2).



results from WP2 and WP3. Obviously, we cannot create valuable guidelines at the end without taking relevant stakeholder views (industry, regulatory authorities, HTA bodies, reimbursement agencies, clinicians, and patient organizations) into account at the beginning and during PREFER. As a result, we will organize several discussion and dissemination activities (eg, a PREFER workshop in Berlin, May 2018, and a PREFER symposium in Basel, July 2019). See the PREFER website http://www.imi-prefer.eu/ for all upcoming events, background information, news, and more.

Because PREFER is currently in its second year, this article will focus on the tasks of WP2 only; the exact approach for WP3 and WP4 is still a work in progress. WP2 consists of eight distinct tasks (Figure 2). Each task is crucial to be able to answer the main research question: "When and how to consider patients' preferences in the MPLC?" For each task, at least one peer-review publication has been planned, including *Value in Health*, and abstracts will be submitted to the European ISPOR meeting in Barcelona, November 2018.

Task 1: What do stakeholders want and need?

Task 1 aims to determine stakeholders' desires, expectations, concerns, and requirements for the assessment and use of patient preferences throughout the MPLC. Hereto, we will conduct (1) a literature review to identify English white literature as well as gray literature, (2) about 150 semi-structured interviews with 6 different stakeholder groups (patients and patient representatives, physicians, academics, industry representatives, regulators, and HTA representatives) from France, Germany, Italy, Netherlands, Romania, Sweden, the United Kingdom, and the United States; and (3) several focus group discussions with patients from Italy, Romania, Sweden, and the United Kingdom as well as with European industry representatives, European HTA representatives, European regulators, and American regulators.

Task 2: Which processes, conditions, and contextual factors influence the utility and role of preference studies in MPLC?

To determine when preference studies are most beneficial in MPLC, Task 2 aims to identify the existing processes, conditions, and contextual factors that have meaningful influence on patient preference assessment and application in decision making along the MPLC by different stakeholders. To address this research question, the same approach as in Task 1 will be used.

Task 3: Where to include patient preference information in decision making?

To ascertain that preference studies provide benefit to decision making, Task 3 aims to (1) identify the decision-making processes and decision points throughout the MPLC for pharmaceutical industry, regulatory authorities, and HTA bodies and payers, and (2) determine critical decision points that have the potential to include patient preference information (PPI). Hereto, we will conduct a scoping literature review and will interview about 70 representatives of 3 stakeholder groups (pharmaceutical industry, regulatory authorities, HTA bodies and payers) from France, Germany, Italy, Netherlands, Romania, Sweden, the United Kingdom, and the United States.

Task 4: What methods exist to explore or elicit patient preferences?
To determine which methods are most promising to explore or elicit patient preferences in the MPLC, a first important step is to identify existing preference methods. The aim of Task 4 is to provide a compendium of patient preference methods (that might have potential) in MPLC. We will conduct a systematic literature review and include at least 20 international experts from different continents in the field of health preference and/or medical decision making to confirm our results and to overcome any publication lag.

Task 5: How to communicate risk, educate patients, and profile psychological variables?
In order to simplify the selection process of educational components in a preference study, it is crucial to develop a catalogue of available psychological instruments and an educational feature-identifier tool. Therefore, the objective of Task 5 is to identify, describe, and assess different approaches to communicate risk, educate patients, and profile psychological variables that can affect the construction, elicitation, and interpretation of patient preferences. Hereto, three scoping reviews for presentation of risk, psychological instruments, and educational tools will be conducted.

Task 6: How to characterize patient preference elicitation and exploration methods?
Before we can determine which methods are most promising to explore or elicit patient preferences in the MPLC, we should first identify important criteria by which to characterize and appraise the patient preference elicitation and exploration methods and determine numerical weights for these criteria for different stages in the MPLC. This is exactly what Task 6 aims to do. In Task 6, we will develop criteria by which to characterize and appraise the methods through incorporating existing criteria from ISPOR guidelines, MDIC's patient-centric benefit-risk framework, and expert stakeholder opinion. Additionally, we will ask health preference experts (including ISPOR members) to complete a Q-methodology exercise to rank all the criteria by importance for several hypothetical scenarios in the MPLC. Finally, an analytical hierarchy process (AHP) will be applied among PREFER and non-PREFER members to determine numerical weights in order to ascertain the relative importance of the criteria.

Task 7: Which patient preference elicitation and exploration methods are most promising?
The objective of Task 7 is to appraise preference exploration and elicitation methods for different stages in the MPLC. First, each preference method identified in Task 4 will be characterized using the criteria determined in Task 6; ie, a table of preference methods by criteria will be prepared. Interviews with health preference experts will be conducted to assess the performance of the methods on these criteria (eg, determine whether certain criteria is met or not for a specific preference method). Second, the numerical weights of the criteria for different stages in the MPLC based on Task 6 will be linked to the data in this table. The AHP will give a score for the utility of each method for each hypothetical scenario, giving rough information on which preference methods are most promising at different stages in the MPLC.

Task 8: When and how to consider patients' preferences in the MPLC?
Finally yet importantly, Task 8 aims to generate a report on "when and how to consider patients' preferences in the MPLC" based on the outcomes of tasks 1 to 7. Additionally, Task 8 aims to provide requirements and both methodological and clinical research questions for the candidate preference methods for testing in WP3's empirical case and simulation studies. While empirical case studies can be used to evaluate how actual patient groups may produce different results for different methods, different stages of the illness, etc., only handful empirical case studies can be performed. The empirical case studies will provide information on the methodological research questions, and as such will generally provide additional evidence. Simulation studies, on the other hand, offer a broad range of possibilities, including the ability to run variations of parameters for different methods thousands of times. Example questions that may be addressed include: How do the preference methods perform when the attributes have disparate utilities versus very similar utilities? How do the preference methods perform when there is considerable uncertainty on utility or considerable population heterogeneity in utility? How similar are the results from different methods as a function of properties of the simulated patient utilities and as a function of changing parameters in the methods?

CONCLUSIONS

The 8 tasks of WP2 will be an important starting point to develop a systematic approach for considering the use of patient preferences across the MPLC. It will contribute substantially to the ideal achievement of PREFER: a global, harmonized approach to the use of patient preference studies by industry, regulatory authorities, HTA bodies, and reimbursement agencies, and, as such, will give patients' preferences a voice in the MPLC.

ACKNOWLEDGEMENT

The Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER) project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115966. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program and EFPIA.

DISCLAIMER

This text and its contents reflect the PREFER project's view and not the view of IMI, the European Union, EFPIA, or the authors' respective organization(s).

REFERENCES

1. PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022. 2017 9/1/2011; Available from: https://www.fda.gov/downloads/ForIndustry/ UserFees/PrescriptionDrugUserFee/UCM511438.pdf. [Accessed April 10, 2018].

2. The 21st Century Cures Act. 2017 December 4, 2017; Available from: https://energycommerce.house.gov/cures/. [Accessed April I10, 2018].

3. Hoos A, Anderson J, Boutin M, et al. Partnering With Patients in the Development and Life Cycle of Medicines: A Call for Action. Ther Innov Regul Sci 2015. 49(6): 929-939.

4. The patient's voice in the evaluation of medicines. 2103, European Medicines Agency.

5. A framework for incorporating information on patient preferences regarding benefit and risk into regulatory assessments of new medical technology. 2015; Available from: http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web.pdf. [Accessed April I10, 2018].

6. de Bekker-Grob EW, Berlin C, Levitan B, et al. Giving patients' preferences a voice in medical treatment life cycle: The PREFER public-private project. Patient. 2017 Jun;10(3):263-266.

7. Levitan B, Hauber AB, Damiano MG, et al. The Ball is in Your Court: Agenda for Research to Advance the Science of Patient Preferences in the Regulatory Review of Medical Devices in the United States. Patient, 2017 10(5): 531-536.

PATIENT ENGAGEMENT

Defining and Measuring Meaningful Patient Engagement: A Multistakeholder Perspective

M. Suzanne Schrandt, JD, Arthritis Foundation and Chair, ISPOR Patient Representatives Roundtable – North America, Atlanta, GA, USA; **Clarissa Cooblall, MPH**, Manager, ISPOR, Lawrenceville, NJ, USA

KEY POINTS

Context can dictate definitions of patient engagement and patient centricity. Therefore, it is critical to know the context in which a given stakeholder is operating, and the definitions that result.

The healthcare system needs to shift from a focus on quantity to a focus on quality, by virtue of patient-engaged value-based practices and payments.

Efforts to measure the value of patient engagement should be exercised with caution, so as to not inadvertently place a higher value "requirement" on patient engagement than on engagement and actions of other healthcare stakeholders.

The past decade has witnessed a seismic shift toward increased patient centricity and patient engagement in research by regulatory and health technology assessment agencies, policy and decision makers, medical technology manufacturers, research organizations, payers and other stakeholders all seeking to understand and incorporate patients' perspectives and experiences into health outcomes research. A wide array of public and private institutions and organizations support patient centricity in research for a number of reasons from enhanced utility and efficiency of clinical trials to societal and ethical obligations. In addition, the involvement of patients or their caregivers in research increases transparency and establishes greater trust in the research process.

As an organization, ISPOR is committed to engaging patients as a key constituency in health economics and outcomes research [see sidebar]. The ISPOR Patient Representatives Roundtable provides a platform for patients and patient advocates to interact meaningfully with other stakeholders, such as researchers, members of industry, and payers. This multistakeholder roundtable deliberates on how patients can effectively participate in research, the development and assessment of new health technologies, and health policy decision making.

The goal of this article is to share the findings from the ISPOR 2017 Patient Representatives Roundtable–North America that focused on eliciting the numerous and sometimes discordant definitions of "patient engagement" among various healthcare stakeholders, as well as identifying the distinct ways stakeholders measure "successful patient engagement".

As predicted, definitions and concepts of measurement and success varied widely and were frequently shaped by the context of the author. The consensus of the group was that it would be valuable to have a summary of the data collected and discussed, as it highlights the challenges and opportunities of patient engagement across the healthcare system.

DEFINITIONS AND CONCEPTS OF MEASUREMENT

The roundtable was comprised of a mixture of key stakeholders, with patient and patient advocates (n=17), patient focused organizations (n=3), academicians and researchers (n=8), regulatory and government representatives (n=4), payers (n=3), and industry representatives (n=4).

The 4th edition of the ISPOR Code of Ethics was published in the December 2017 issue of *Value in Health*. This updated document is intended to better address issues that have arisen in the era of today's rapidly evolving digital heath environment, namely the role of the patient in research.

This edition of the Code of Ethics includes an entirely new chapter on Patient Centricity and Patient Engagement in Research. The content includes guidance on a wide range of patient-related issues, including patient confidentiality, informed consent, data sharing, and the proliferation of different routes for digital dissemination of health economic information, as well as more traditional areas such as research study design, publication and sponsorship.

Patient-related chapter materials and appendices include:

- Understanding Patient Centricity and Patient Engagement (Chapter 7)
- Levels and Timing of Patient Engagement
- Partnering with Patient Organizations
- Ethical Considerations
  - Primary Research Means of Recruitment (Appendix 5)
  - Considerations for Research Participant Involvement in Research Development and Design (Appendix 10)

For more information on the ISPOR Code of Ethics, go to https://www.ispor.org/CodeOfEthics-guideline.pdf?v2.

Figure 1. Components of Defining Patient Engagement

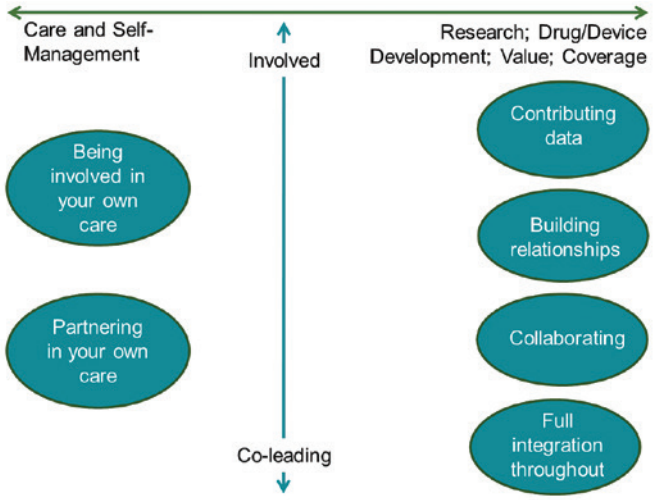
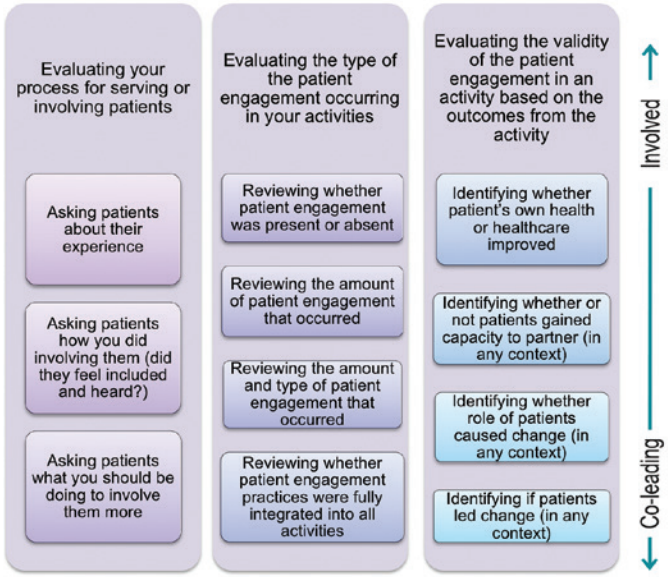


Figure 2. Domains of Measurement for Patient Engagement



Prior to the in-person gathering, all roundtable participants were asked to respond to a set of questions that addressed meaningful patient engagement. These questions focused on how meaningful patient engagement was defined by the organizations and how they determined if their engagement efforts were successful. Additionally, organizations were asked for an example of how they measured the impact of meaningful engagement. After a presentation of the findings, participants were divided into 3 breakout groups to discuss existing measurement tools and the potential for a unified way to measure patient engagement.

Defining Patient Engagement

Participants represented many different facets of the healthcare system and therefore the answers to the "definition" questions were found to be context-driven. The responses grouped loosely into 5 domains: (1) care and self-management, (2) research, (3) drug/device development, (4) value, and (5) coverage.

However, there was a clear distinction between the nature of the definitions that centered around care and self-management versus all other domains. Patient engagement, as defined in the care and self-management domain, related to the ability and willingness of a patient to be active and motivated in his or her own care. Conversely, across the other 4 domains, patient engagement was defined to be the involvement of patients across different activities across the healthcare system—not the involvement of patients in the management of their own diseases/conditions.

The disconnect between these two interpretations of the patient engagement definition is not unique to this group, but the diverse composition of the roundtable and the complexity of the answers provided, yielded additional insights into why the disconnect exists. While patients are encouraged to be active partners in their care and disease management (definition 1), in order to be actively engaged as partners in the healthcare system (definition 2), it is critical to know which definition is implied in a given context. As a promising practice, any time a patient engagement initiative is begun, all involved parties should identify up front how they are defining patient engagement for purposes of their work.

The responses also appeared to use different constructs for the role of a patient. On one end of the continuum, the patient was "involved" but not an equal partner, and on the other end, the patient was "co-leading" or "leading" the process (Figure 1). For example, within the care and self-management domain, the two ends of the spectrum are "being involved" and "leading or co-leading". The majority of the answers clustered around "being involved in your own care" or "partnering in your own care" as reflected in the two spheres in the graphic. In the research domain, a similar continuum surfaced spanning patients "contributing data" to patients "collaborating and being fully integrated" in the research process. The conversation highlighted how critical it is to understand where stakeholders are coming from and in what circumstances they are operating as that largely dictates how they think and feel about—and operationalize—patient engagement.

Measuring Patient Engagement

The discussion around measurement again gravitated toward context, with 3 domains emerging, each dependent on how and where a stakeholder was positioned. As with the definition exercise, the responses also tended to plot along a continuum of patient inclusion, with one end capturing patients as "involved" but not as equal partners, and the other end describing patients "co-leading" or "leading" the process. Specific examples are provided across the 3 domains on the scale from "involved" to "co-leading" (Figure 2).

Summary of Breakout Group Sessions

Groups discussed the potential for all key stakeholders to convene and find a unified way to measure patient engagement. Participants encouraged the development of a tangible product such as a checklist or tool to measure engagement that would be useful and adaptable across a diversity of stakeholders. These stakeholders should be involved in the creation, implementation, and dissemination of the tool or checklist. Other suggested key characteristics of the checklist or tool included having a flexible framework that is transdisciplinary, multidimensional, and interoperable for different applications of use. The tool >

should include characteristics of robust engagement and examples of engagement activities that users can benchmark against to validate the strength of their engagement efforts. An evaluation component to the tool is necessary (including a way to measure incremental, mid-term, short-term, and long-term impacts), especially in addressing the need to cycle information back to patients as a part of engagement. Patients should be made aware of outcomes and results any time they are involved in a research and/or a decision-making process.

Participants discussed the applicability of tools to measure patient engagement and identified a few issues and gaps that have hindered its success. These challenges include a lack of knowledge about what types of patient-related data are actually reviewed by assessors and decision makers, and how patient perspectives can best be captured in value frameworks.

> ...in order to be actively engaged as partners in the healthcare system it is critical to know which definition is implied in a given context. As a promising practice, any time a patient engagement initiative is begun, all involved parties should identify up front how they are defining patient engagement for purposes of their work.

KEY LEARNINGS AND IMPLICATIONS

A sentiment that emerged among the responses during and prior to the roundtable was a sense of caution around the act of defining "success" in patient engagement. The group acknowledged that there tends to be a desire to hold patient engagement to a far higher standard than other aspects of healthcare and research, and in defining success and instituting measurement, we do not want to inadvertently create unattainable goals. Additionally, it was noted that other healthcare and research stakeholders are often assumed to be providing value—just by their participation in a given process. We want to be cautious that we are not setting the precedent that patients must *prove* their value by measuring it, whereas other stakeholders' value may not need to be measured.

In terms of the "added value" of patient engagement, it was proposed that if patient engagement activities are not seen as adding value, then it is probably because we are not finding the right ways to make that engagement *meaningful*. To that end, many participants spoke to the need to help newer or less involved patient advocacy organizations advance along the advocacy and engagement curve. Models and training programs have been created to try to meet people "where they are" and then translate their experience, either into a policy agenda or into research activities. This support and insight can help to facilitate a patient advocacy organization's engagement prowess.

The participants recognized a need to measure patient engagement through an outcomes-based process versus an outputs-based process, such as capturing patient outcomes versus capturing the number of patients engaged in a given activity. For the vast majority of patients who are not routinely interacting with industry or academia, it may be more prudent to measure patient engagement at the practice level, via patient satisfaction scores, shared decision-making, and other patient preference incorporation.

While much of the group discussions focused on the above topics, a few new concepts and needs emerged. One issue was the need to better streamlined the use of patient-reported outcomes across more facets of the healthcare and research system so that data capture during one "phase" is useful—and is used—during other phases. Additionally, the need for more patient engagement in the "value" and value framework space was discussed. Identifying the best ways to incorporate inclusion of patient perspectives in value conversations is critical and while many organizations have put forth rubrics and models, fostering uptake of these best practices remains difficult.

Finally, participants were asked to identify what would be the most useful and tangible outcomes from the roundtable. The consensus of the group was that there were currently many activities underway (including the function of the ISPOR Patient Centered Special Interest Group) and that a white paper summarizing the day's discussion and the many ideas and goals for defining and measuring patient engagement would be the most productive. Other calls to action included the review of the ISPOR Patient Centered Special Interest Group definitions for patient engagement, patient centricity, and related terms, and to organize a dissemination plan. Participants suggested that the forthcoming definition of patient engagement from ISPOR would be foundational to future work.

ACKNOWLEDGEMENTS

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Additional information

For more information on the ISPOR Patient Representatives Roundtable, please visit: https://www.ispor.org/councils/Patient_Representatives_Roundtable.asp. and the ISPOR Patient Centered Special Interest Group at https://www.ispor.org/sigs/PatientCentered.aspx.

For more information on the ISPOR Patient Centered Special Interest Group definitions for patient engagement, patient centricity, and related terms, view the group's presentation from the ISPOR 22nd Annual International Meeting at https://www.ispor.org/sigs/Poster_PatientCenteredSIG_DC2016_.pdf.

PATIENT ENGAGEMENT

Decision Making Across the Healthcare Continuum—The Path Forward Is Patient-Powered

Robert N. McBurney, PhD, Accelerated Cure Project for MS and iConquerMS™ People-Powered Research Network, Waltham, MA, USA; **Heather Siefers, BS, MS**, iConquerMS™, Rockville, MD, USA; **Richard Rudick, MD**, Biogen, Inc, Cambridge, MA, USA; **Amy Phillips, PharmD**, EMD Serono, Inc, Rockland, MA, USA; **Laura Kolaczkowski**, iConquerMS™ PPRN, Dayton, OH, USA; and **Kristin Mulligan**, Feinstein Kean Healthcare, Cambridge, MA, USA

KEY POINTS

More organizations are working to make patients truly central to decision making, in new ways that go beyond conventional focus groups or one-time surveys.

Outcomes-based contracts, the collaborative efforts between payers and manufacturers that focus on performance solutions to help assess value, are a structure already in place that could be utilized for better patient integration in healthcare decision making,

Whether through consortiums, continuously expanded sources of real-world evidence, or the promising model of Patient-Powered Research Networks (PPRNs), it's clear that the future is networked and must include the direct input of those at its center—the people living with chronic conditions in need of clinical care.

In this article, members of the MS patient, research, and clinical communities share insights on the path forward for patient engagement in healthcare, including models and frameworks for a more sustainable, networked approach to incorporating the patient "voice" across the healthcare continuum.

Across the healthcare landscape, there has been a deepened "focus on the patient." Yet a gap often remains between the wide variety of symptoms that people living with a given health condition experience and the current treatment-response outcome measures that are the focus of regulators, drug developers, and healthcare technology assessors. Important progress is being made to collaborate and integrate patients with technology assessment, drug development, and research processes more effectively, but much of this integration is happening through "one-off," one-way requests or projects.

PROGRESS UNDERWAY

More organizations are working to make patients truly central to decision making, in new ways that go beyond conventional focus groups or one-time surveys. One case study shared at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 22nd Annual International Meeting in May 2017 described efforts by the Critical Path Institute, a public-private partnership focused on accelerating medical treatments by developing tools for clinical studies. The Institute's Multiple Sclerosis (MS) Outcome Assessments Consortium developed the first data standard for MS, allowing data that have been collected across distinct clinical trials to be pooled for evaluation. The standard included a deepened analysis that combined these trial results with input from people living with MS on clinical measures (and identification of gaps in these measures) related to impact on real-life activities and lifestyle [1].

> The true potential of patient engagement will center on a more structured, consistent system of relationships between stakeholders across decision-making processes in healthcare. Stakeholders representing the "patient voice," as well as those in industry and other areas, must develop these structures to enable sustained, productive engagement.

The true potential of patient engagement will center on a more structured, consistent system of relationships between stakeholders across decision-making processes in healthcare. Stakeholders representing the "patient voice," as well as those in industry and other areas, must develop these structures to enable sustained, productive engagement. Further, it is important that this voice entails not only opinions but also rigorously collected data about symptoms, abilities/disabilities, and quality of life that meaningfully affect care. As we envision how these systems might take shape, there are innovative early examples and frameworks to consider as potential models for patient engagement, including new clinical study protocols, data standardization measures, and People-Powered Research Networks (PPRNs.)

Additionally, medical and pharmacy claims data, patient survey data, electronic health records, data from mobile apps and wearable devices, and even social media content are just some of the channels contributing to real-world evidence (RWE), >

now being tapped into by pharmaceutical and medical device companies for insights on disease burden, patient care, and treatment and products. Content from these sources is even being published increasingly in medical literature [2]. The number of formal patient registries by health condition is also growing, enabling researchers and other stakeholders to gain insights into budget impact and post-marketing commitments such as safety, adherence, sub-populations, and treatment switching patterns.

There is even change underway regarding how "patients" are referred to these days. More organizations focused on specific health conditions or therapeutic areas are engaging with "people with MS," or "people affected by MS," for example, to address not only those diagnosed with the disease but also caregivers, family and friends. This also reflects a shift from viewing patients as passive subjects for whom medical products and treatment protocols are developed and trialed "on," or "for," to fully engaged participants—people—to be collaborated with, and who are not defined only by their health condition. For simplicity within this article, we refer to "patients" to define the broad group's stakeholders with various health conditions we are discussing, but it is important to acknowledge that increasingly, this term is being replaced.

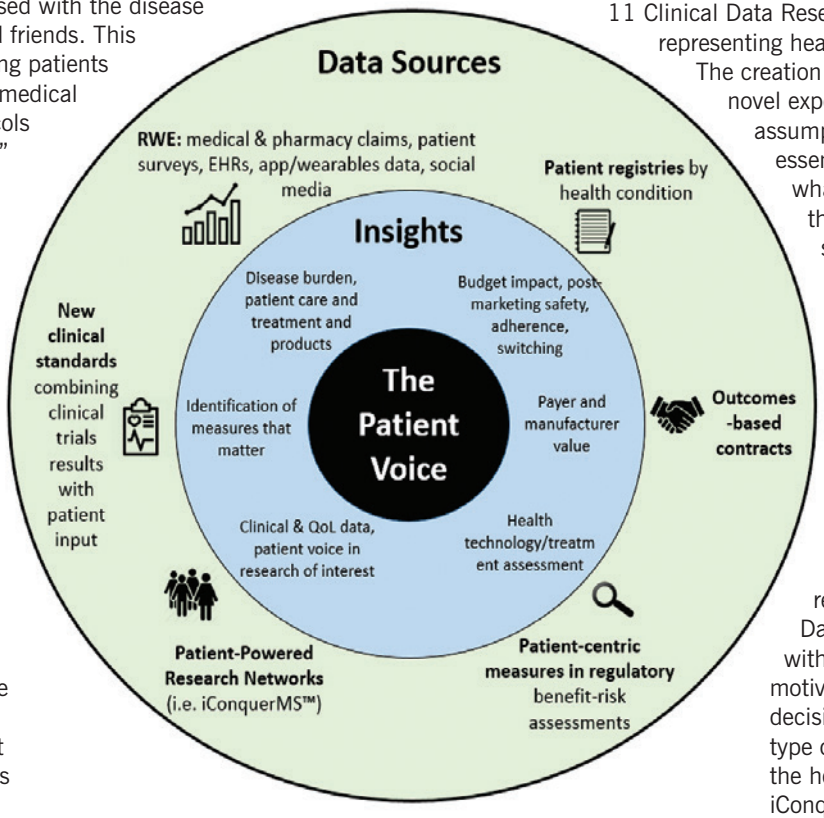
MODELS AND CHANNELS FOR CONSIDERATION

Outcomes-based contracts, the collaborative efforts between payers and manufacturers that focus on performance solutions to help assess value, are a structure already in place that could be utilized for better patient integration in healthcare decision making, such as pulling in the patient voice through payer and manufacturer value assessments. With the increase in innovation and the use of technology, are there opportunities to capture patient survey data, through either mobile apps or even adherence trackers? How can data from patients and information about their perspectives and what is important to them be incorporated into health technology assessment? Opportunity exists to leverage some of the healthcare structures that are in place now to start answering these questions.

Another model for integration of patient-focused metrics in regulatory processes exists in the Medical Device Innovation Consortium (MDIC)'s Patient Centered Benefit Risk (PCBR) project, developed in response to guidance from the FDA calling for more patient-centric measures in regulatory benefit-risk assessments. A public workshop convened a cross-section of experts to develop a first-of-its-kind framework and catalog of patient reference methods [3]. This type of patient preference assessment is in its very early days as a scientific discipline, but presents a framework for medical device companies to use today and can be built on and expanded to other spaces.

A POTENTIAL PATH TO PATIENT-CENTRICITY ACROSS THE HEALTH-CARE CONTINUUM: PPRNS

Another channel for integration of the patient voice are Patient-Powered Research Networks (PPRNs). PCORnet, a national network for conducting patient-centered outcomes research to improve healthcare, comprises 20 PPRNs linked to 11 Clinical Data Research Networks (CDRNs) representing healthcare provider systems. The creation of PPRNs has been a novel experiment, centered on the assumptions that patients are the essential source of knowledge of what is important to life with their condition, and that they should drive research directly and articulate the measures that matter most.



Data-driven sources, insights, and frameworks for putting patients at the center of healthcare decision making and research

EHRs=electronic health records; RWE=real-world evidence.

The iConquerMS™ initiative is an important PPRN in the MS space, led by the Accelerated Cure Project, a nonprofit organization that collaborates with people living with MS, other leading MS advocacy organizations, researchers and clinicians. Data has shown that people with MS may be particularly motivated to participate in medical decision-making [4]. Indeed, this type of engagement has been at the heart of the success of the iConquerMS™ initiative to date. Since its kick-off in 2014, more than 4,000 people have enrolled and begun to participate in research through the network.

iConquerMS™ is governed by a majority of people with MS, and engages with its community to power—and to shape—what is studied and learned about MS. Participants complete standardized surveys on a regular basis to provide researchers and other stakeholders with data, including demographics, health history, symptoms, abilities/disabilities, and quality-of-life measures. This information may yield patterns and insights to uncover the causes of MS or reveal who may respond best to various therapies or new treatments. Importantly, patients can also shape research by suggesting topics for study or study design.

iConquerMS™ survey data have found that many symptoms, such as fatigue, sleep disturbance, anxiety, and depression, affect people with the relapsing-remitting form of MS more severely than lower

extremity functional abilities. However, most regulatory clinical trials do not routinely assess the most affected symptoms as primary or secondary outcome measures, instead focusing on the frequency of relapses, a disability scale that relies heavily on lower extremity function, or on features of magnetic resonance images. Addressing the disparity between what affects people with MS the most and the status of outcome measures used in clinical trials is a clear need being articulated by the "patient voice" as reflected by data on symptoms, abilities/disabilities, and quality of life.

THE PROMISE, PURPOSE, AND PATH FORWARD FOR PPRNS

To date, MS drugs in development have been tested primarily for their impact on objective clinical measures alone. Yet it is important to also include other factors that matter to patients. The research that a PPRN such as iConquerMS™ can catalyze has the potential to span the healthcare continuum by:

- Helping define and measure the quality-of-life parameters that should be considered when therapy is chosen
- Fueling development of interventions and tools (digital or otherwise) that help patients to sustain their quality of life
- Identifying what attributes are desired in a new drug
- Driving the integration of endpoints into clinical development that measure the impact of a certain drug or treatment
- Measuring the RWE of a marketed drug concerning how it is performing in large numbers of patients

Strides have been made, yet much remains to be done to evolve patient centricity from an aspirational ideal to concrete protocols adopted as a standard practice across the health sector. Stakeholders must move away from "one-off," directive projects to gather patient input on a single topic—a one-day focus group for feedback on a medical device company's planned messaging or advertising for a product launch—to a longer-term engagement across industry, regulatory, advocacy, and third-party organizations representing patients. Although still nascent, frameworks for a more sustained and data-driven structure for such engagements are emerging. Whether it be through consortiums, continuously expanded sources of RWE, or the promising model of PPRNs, it's clear that the future is networked and must include the direct input of those at its center—the people living with chronic conditions in need of clinical care.

REFERENCES

1. Critical Path Institute. Multiple Sclerosis Outcome Assessments Consortium. Available at: https://c-path.org/programs/msoac/. [Accessed December 14, 2017].

2. Risson V, Saini D, Bonzani I, et al. Patterns of Treatment Switching in Multiple Sclerosis Therapies in US Patients Active on Social Media: Application of Social Media Content Analysis to Health Outcomes Research. J Med Internet Res 2016;18(3):e62.

3. Ho, Martin, et al. A Framework for Incorporating Patient Preferences Regarding Benefits and Risks into Regulatory Assessment of Medical Technologies. Value in Health. September 2016. Volume 19, Issue 6, 746-750.

4. Hamann J, et al. Health Expectations, 10:358-363.

RARE DISEASES

The Patients' Voice in the Evaluation of Orphan Drugs

Benoit Arnould, PhD; Mapi, an ICON plc company, Lyon, France; **Sheela Upadhyaya, HDN**, NICE, London UK; **Charlotte Roberts, BA**, MPS Commercial, Amersham, UK; and **Samantha Parker, MBA**, Lysogene, Neuilly sur Seine, France

KEY POINTS

Patients' testimonies offer an additional perspective on rare diseases and their treatment and can provide information that is not captured by clinical trial assessments.

Mixed-methods research, combining qualitative and quantitative research within the same program, can be used to integrate the patient perspective into clinical research programs.

The NICE Highly Specialised Technology appraisal program provides an example of how patients' submissions can be incorporated into the decision-making process of health technology assessment bodies.

CHALLENGES FOR PATIENT-CENTERED OUTCOMES RESEARCH IN RARE DISEASES

The difficulties of working with rare diseases mean that researchers, payers, and health technology assessment (HTA) bodies may have to make decisions about orphan drugs based on limited information, particularly with respect to patient-reported outcomes (PROs). This is important given the profound effect that rare diseases can have on patients' lives.

There are a number of challenges for PRO research in rare diseases. The number of patients is limited, generic measures may not be valid or responsive enough for rare conditions, self-reporting may be difficult due to the patient's age or cognitive impairment, and disease-specific measures can be costly and time-consuming to implement. Moreover, the range of possible evaluations can be complex (e.g., symptoms, functioning, quality of life, caregiver and family burden, and valuation across different age groups or disease stages). Consequently, HTA bodies often receive dossiers that lack essential information concerning PROs. Greater efforts are needed to systematically include the patients' perspective in the evaluation of orphan drugs.

One approach is to use mixed-methods research [1], whereby qualitative research is combined with quantitative research within the same program (see Table 1). This framework can be used to integrate the patient perspective into clinical research programs, with relatively small increases in costs and the burden for researchers and patients.

At present, the patient's voice is largely transmitted in the form of testimonies. Key issues include the extent to which testimonies affect HTA decisions, whether this is sufficient to ensure reliable decision making and if not, whether qualitative research (combined with quantitative research) would fill the gap.

Table 1. Mixed-Methods Research

Definition	"Research in which the investigator collects and analyzes data, integrates the findings, and draws inferences using both qualitative and quantitative approaches and methods in a single study or a program of inquiry." [1]
Potential	Well-designed mixed-methods research combines the advantages of qualitative and quantitative research methodologies: - Qualitative research (e.g., patient interviews and thematic analysis) is good for exploration. It is affordable, flexible, rich, powerful, and conveys accessible messages. - Quantitative research (e.g., drug efficacy in clinical trials) is good for hypothesis testing and evidence generation. It is reliable and well accepted for supporting decision making.
Applications in clinical development	STRATEGY - Identify needs and priorities (burden of illness) - Understand treatment benefits (concept of interest) - Signal detection METHODOLOGY - Test content validity of a specific patient-reported outcome measure - Develop conceptual models - Set foundation for instrument adaptation or development EVIDENCE GENERATION - Inform endpoint selection and choice of measures - Individual risk/benefit assessment - Goal definition and attainment

THE HTA PERSPECTIVE

How do testimonies from patients or their representatives impact HTA decisions? Is this reliable enough to support decisions from a public health perspective?

The Highly Specialised Technology (HST) appraisal program at the National Institute for Health and Care Excellence (NICE) evaluates ultra-orphan conditions and is unique in the way it includes patients within the process. Decision making centers on an assessment of value and takes into account the nature of the condition, the impact of the new technology, costs to the National Health Services (NHS) and social services, value for money of the product, indirect and non-health benefits, and delivery of any specialized services. The appraisal process involves three stages: scoping, evaluation, and guidance development. Patients are involved in all stages and participate in associated meetings. During scoping, patients and patient groups can provide clarity on patient numbers, current treatment regimens, and best supportive care, as well as details of the condition and outcomes that should be considered. During the evaluation stage, patient testimonies are sought, together with further clarification of patient numbers and patient experiences with the condition and the new drug. Patients and patient groups are then invited to comment on the draft guidance to ensure that their submitted information has been represented accurately.

Patients and patient groups are provided with a template and guidance on how to submit information. A lay member of the HST Committee then summarizes submitted testimonies into slides for presentation at Committee meetings, during which the patients and patient groups check whether the information has been presented accurately and whether the Committee has understood it correctly.

Patient experts are individuals with experience of the broader patient population relevant to the evaluation and/or relevant personal experience. Their role is to provide statements which will help the Committee consider key criteria such as the nature of the condition and burden of disease. They also attend Committee meetings as individuals.

From the HST's perspective, patients are able to bring the condition to life for the Committee. Their input is of value for defining and clarifying the patient population and numbers, the burden of disease, what is important to patients, which patients will benefit most, the impact of treatment, the likely uptake of treatment, and whether there might be adherence issues.

Although the HST values patient input and considers it interesting and important, challenges remain. There is frequent discussion about whether patient submissions are evidence or testimony. Is there actually a need to quantify the information? And what quality assurance mechanisms should be deployed around the delivery of the information?

THE PATIENTS' PERSPECTIVE

How do patient representatives communicate with HTA bodies? To what extent do HTA bodies listen to the voice of the patients, their families, and their representatives?

In the United Kingdom, patient organizations contribute to HST evaluations in several ways. They attend scoping meetings, identify patient experts to write submissions and attend HST Committee meetings, support and counsel patient experts, and encourage the wider patient community to respond. They also provide information on patient numbers and can identify patients across the spectrum of the disease to participate in the process.

Whereas patient organizations have a broad knowledge about the disease and the impact of the drug, patient experts have first-hand experience. Patients involved in the HST process need to be supported because of the demands it places on them in terms of emotions, time commitment, sense of responsibility, and exposure to confidential information. Despite their inevitable emotional involvement, the voice of patients should carry weight.

> Greater efforts are needed to systematically include the patients' perspective in the evaluation of orphan drugs.

It is difficult to quantify the extent to which HTA bodies listen to this voice, but patients do give an additional perspective and may be able to provide information not captured by clinical trial assessments. In particular, quality-of-life data can be difficult to capture but often has the greatest impact on patients. Patients can also refute incorrect perspectives. For example, patients involved in the HST evaluation of a treatment for mucopolysaccharidosis (MPS) IVA (Morquio syndrome) were able to provide examples of how treatment had increased their energy levels, something that was not necessarily captured by clinical trials' data. In addition, although increased wheelchair use was considered a negative outcome, one patient explained that she had started using a wheelchair because she now felt well enough to go out socializing, which she had not done previously.

The MPS Society, a patient organization for mucopolysaccharide disease, was involved in the development of the first Managed Access Agreement. This novel scheme was set up to enable treatment to be provided to patients with MPS IVA who derived benefit from it, while discontinuing it in those who did not, and to gather long-term data on treated patients. The Managed Access Agreement was written in collaboration with NHS England, NICE, a pharmaceutical company, an expert clinician, and the patient organization. Patients with MPS IVA who met the eligibility criteria agreed to attend 4 assessment visits within the initial 14 months and to complete quality-of-life questionnaires every 4 months for 5 years. Treatment will be withdrawn after 1 year for patients who are not compliant or do not meet 4 out of 5 predetermined clinical criteria. While the program is underway, the MPS Society has been communicating separately with patients receiving the treatment and has identified some benefits that are important for patients but have not been captured by the quality-of-life tools used for the Managed Access Agreement. Examples include increased energy, strength, and mobility, as well as improved sleep, less pain, and increased independence.

This illustrates that despite their emotional involvement, patients provide insight into the benefits of treatments beyond clinical trial measurements and play a key role in the decision-making process. >

THE INDUSTRY PERSPECTIVE

How do pharmaceutical companies capture the patient perspective when developing therapeutic innovations? How do they align their endpoint strategy to patient needs and priorities?

It can be difficult to evaluate some clinical endpoints in rare diseases using standardized assessment tools. In particular, in the field of pediatric neurodegenerative diseases, the target alters depending on the age of the child. For example, children with MPS IIIA show normal development until the age of 1 to 4 years, after which they regress in terms of behavior and cognition and develop major hyperactivity and sleep disorders. This has a substantial adverse effect on the quality of life of patients and their families. To make things more complex, currently there is no biomarker for the disease to use as a surrogate marker of clinical outcome. This means that researchers have to assess somewhat intangible effects of drugs.

In a Phase I–II gene therapy trial, the clinical assessment tools used to evaluate disease progression were exploratory and not optimal in terms of comprehensiveness, specificity, and meaning for patients and their families. However, the patient community for this disorder is small, and the researchers became aware of indirect testimonies that the treatment was having an effect on sleep and hyperactivity. This illustrates how important it is to capture the patient's perspective.

Companies developing treatments for rare diseases need to make their activities patient-centric and gain a broader understanding of the impact of the disease and treatments on patients and their families. This can be done in several ways. Patient organizations can be involved in the design of the protocol, study inclusion criteria, and recruitment strategy. Researchers working on rare diseases can attend patient group discussions, where they might hear useful anecdotal information about small issues that are not covered in publications. Facebook and Twitter also can be useful in this respect. Testimonies from clinical trial participants provide additional information that can be helpful.

Semi-structured interviewing is a technique that may be able to help clarify the patient's perspective. It is currently being used as part of a natural history study in MPS IIIA to look at specific aspects of the disease that were identified as being troublesome based on the testimonies of participants of an earlier clinical trial. Sleep and behavior were identified as particular problems. Although sleep can be quantified as part of a trial, this does not address the wider effect that disordered sleep might have.

The objectives of the semi-structured interview are: to capture meaningful aspects of the disease and how it affects the patient and family life from the parents' perspective; to cover specific areas related to the MPS IIIA clinical phenotype and how these change over time; to explore thoughts and feelings not picked up by the standardized assessment tools used in the study; and to collect data that could be used as a control in future clinical trials.

Rigorous methodology is needed in order to ensure data quality. A specific interview guide was developed and included in the study protocol. The interviews are conducted face-to-face, last 60 minutes, and are performed by external psychologists or researchers who have undergone training on the disease and the aspects of interest. They are audio-recorded, which allows the interviewer to pay full attention to the parent, and enables auditing to be performed. The interview is designed to be exploratory and capture the parents' own words and spontaneous expressions; it involves open discussion, with no direct questions. Transcripts are analyzed using software specifically designed for qualitative analyses. This allows traditional qualitative analysis and facilitates the breakdown of qualitative data into groups.
The results are not available yet, but it is hoped that this approach will provide a way of bridging the gap between testimony and quantitative measurements.

REFERENCES

1. Tashakkori A, Creswell JW. The New Era of Mixed Methods. J Mix Meth Res 2007;1(1):3-7.

Additional information

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

RARE DISEASES

Why Does the European Commission Prefer to Sponsor Agriculture Production Than Support Patients' Access to Orphan Drugs?

Katherine Young, MD, MPH, MSc, Creativ-Ceutical, Paris, France; **I. Soussi, MSc**, Creativ-Ceutical, Tunis, Tunisia; and **Mondher Toumi, PhD, MD, MSc**, Aix-Marseille Université, Marseille, France

KEY POINTS

External reference pricing has become the most common price setting measure for pharmaceuticals in EU. All regulations, even if justified, may have a perverse effect. The perverse consequence of ERP is the acceleration of access and lower orphan drugs net prices in high-GDP EU countries while delaying or preventing access and higher net prices in low-GDP countries

Our study which compared the relative prices of orphan drugs in 12 European countries validated that when the country's ability to pay was taken into consideration, lower GDP countries paid relatively higher costs for similarly available orphan drugs in Europe

This unacceptable inequity must be urgently addressed at the EU level, in the same manner that the EU was able to address concerns in the agricultural sector

Various studies in the literature have investigated the relevant issue of inequitable access of drugs in Europe. The 2016 IHE comparator paper reported the unequal access to oncology treatments between low and high gross domestic product (GDP) per capita countries. Per the report, Eastern and Southern Europe's oncology drug sales were approximately only a third of the sales in Western Europe, from 2005 to 2014 [1]. Another study in 2016 [2] looked at the affordability of hepatitis C treatments sofosbuvir and ledipasvir in 30 countries and showed that Central and Eastern European countries had higher purchasing power parity (PPP)-adjusted prices, indicating that low- to median-income countries may be paying relatively higher costs than economically stronger countries rendering lower affordability and lesser access to innovative treatments. Orphan drugs, medicines intended for the prevention or treatment of rare diseases, are central to discussions on high drug prices and low health equity. Rare diseases are usually severe conditions with no or limited choice of therapeutic options, and thus present with a high level of unmet need. The equitable access to innovative medicines that are able to offer better outcomes is imperative for these patients.

> Our results validate that the current EU policy has a low ability to align access to orphan drugs across different Member States, resulting in inequity between richer and poorer countries across the European Union.

External reference pricing (ERP) is the most common price-setting measure for pharmaceuticals in EU member states (MS). ERP, which is also known under different names such as external price referencing (EPR), international reference pricing, or international price comparison/benchmarking, is defined as "the practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country." [3] ERP's rationale is to ensure that unfounded price gaps are not excessive among countries within a similar region with the same ability to pay. However, it has also become widely used in the EU to avoid parallel trade as a result of the free movement of goods. Differences in prices between states may cause the importation of drugs from low-priced countries to high-priced countries, which may lead to drug shortages in low-priced countries [4]. As such, pharmaceutical companies continuously utilize ERP rules within their strategies to prevent parallel trade by having similarity in the absolute prices among neighboring countries. No objective and comprehensive literature has been found assessing to what extent ERP is used in orphan drug pricing in Europe. In the same manner, no evidence has been found to show that ERP is not used in orphan drug pricing. As such, it is a fair assumption that orphan drugs are subject to ERP mechanisms like other pharmaceutical products.

In Europe, 29 of the 31 countries apply ERP as a price regulation tool and thus, theoretically, should lead to price convergence in Europe (the United Kingdom and Sweden do not use ERP) [5]. Indeed, ERP may have converged the absolute prices of orphan drugs but may have caused relative costs to differ because purchasing power is not taken into account in ERP price calculations and also is not accounted for in the selection of reference countries [4]. All regulations, although justified, may have a perverse effect. The perverse consequence of setting ERP regulations in the MS may >

be an acceleration of access and lowering of orphan drugs net prices in high-GDP countries while delaying or preventing access and increasing net prices in low-GDP countries.

ERP coexists with confidential discounts in high-volume countries (usually the richest) and low discounts in low-volume countries (usually the poorest). This may lead to lower net prices in the richest EU countries compared to the economically challenged ones. High-GDP countries have greater payer negotiation powers compared to low-GDP countries due to their size, revenue, and purchasing power. Rebates are confidential and not published, and thus will not be integrated in ERP rules. Ex-factory price, the most used reference in ERP [5], does not reflect the final price after confidential negotiations between payers and manufacturers. This may result in lower GDP countries referencing inaccurately higher prices, which adds additional cost burden. From the authors' experience, rebates do exist in lower GDP countries in the European Union but to a lower magnitude than in the highest GDP countries. Manufacturers are also noted to use launch sequence strategies to avoid initially launching in countries with low price potential, thus avoiding the consequence that the low list price will inevitably be referenced by bigger markets [5]. Launch may then be delayed in low-GDP countries. This further limits access to innovative and potentially life-saving treatments.

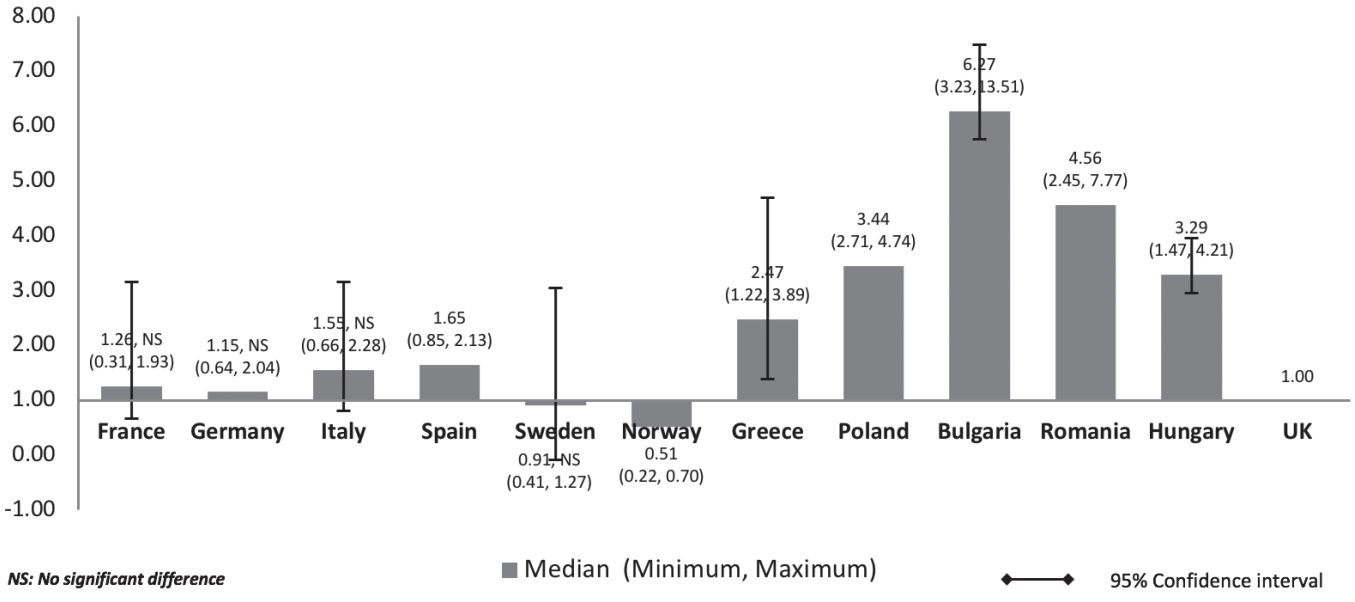
The European Commission, Ministries of Health of MS, and relevant European organizations have voiced concerns regarding health inequity and inaccessibility of orphan drugs to vulnerable populations [6,7]. As a possible solution to address these concerns, several discussions on differential pricing (DPR) have joined the narrative but this was never implemented because it was found to be too challenging [8-10]. DPR "is based on the economic concept of price discrimination whereby prices of the same products are variedly set for different consumer groups in different geographical or socio-economic segments based on the income or purchasing power of those buyers [11]."

In the agriculture sector, the European Union has been able to put in place the Common Agriculture Policy (EU-CAP), a complex and expensive compensation system that leads to the differential pricing of agricultural goods, but which consequently benefits a large and rich EU country like France. The EU-CAP guarantees a stable, fixed price of agricultural products throughout the European Union, which avoids visibility and speculation among producers. As the market price of the products is often below the guaranteed price, the European Union pays the producers the deficit as a form of compensation. France captures 60% of this money. This means that instead of investing in economic changes and future revenue, the European Union is investing in covering the deficit of agricultural producers who are producing at a cost that is significantly above the market price. The EU-CAP represents around 50% of the EU budget. The question that needs to be asked is why such framework is considered unfeasible for orphan drugs.

The European Union has considered multiple options for how to resolve the unacceptable inequity, from differential pricing with compensation, to EU global procurement for all MS and the distribution at a differential price even though the listed price is uniquely fixed, a similar process as the EU-CAP. These were never implemented. The EU can procure centrally and charge the MS based on their affordability while setting a fixed pan-European list price. Ultimately, this will implement a differential pricing scheme while avoiding parallel trade at the same time.

In more recent years, the inequitable access to orphan drugs has increased significantly as the prices have soared and the affordability in lower GDP countries has plunged. To appreciate this issue better, we did a study where we assessed the affordability of orphan drugs in 12 European countries [12]. The study

Figure 1. Relative cost ratios adjusted using nominal GDP per capita (UK reference = 1)



compared the relative cost differences of similarly available orphan drugs among high- and low-GDP countries in Europe: Bulgaria, France, Germany, Greece, Hungary, Italy, Norway, Poland, Romania, Spain, Sweden, and the United Kingdom. Annual treatment costs per patient were calculated then adjusted by nominal GDP per capita, GDP in PPP per capita, percent of GDP contributed by the government, government budget per inhabitant, percent of GDP spent on healthcare, percent of GDP spent on pharmaceuticals, and average annual salary. An international comparison of the relative costs was done using the United Kingdom as the reference country and results were analyzed descriptively.

Our results show that the median annual costs of orphan drugs in all countries varied minimally. However, when the annual costs were adjusted using GDP per capita, the lower GDP countries showed three to six times higher relative costs (Figure 1). High-GDP countries maintained minimal differences. Differences were significant for all except between the United Kingdom and France, Germany, Italy, and Sweden (higher GDP countries).

The same pattern was evident when costs were adjusted using the other economic parameters. When the costs were adjusted using average annual salary per inhabitant, the lower GDP countries showed higher costs than high-GDP countries by a factor of around 3 to 9. This means that an average individual in lower GDP countries will have to work nine times more (Bulgaria) than their western counterparts in order to afford the same drug. Drug spending in low-GDP countries is mostly out of the pocket, which exacerbates affordability issues. GDP share contributed by the government and government budget per inhabitant shows the lower per capita spending by the government in low-GDP countries resulting in higher relative costs per patient, lower ability to pay, and limited access to orphan drugs for rare diseases that lack alternative treatment.

Our results validate that the current EU policy has a low ability to align access to orphan drugs across different Member States, resulting in inequity between richer and poorer countries across the European Union. The European model upholds the principle of equity and solidarity where the richer population subsidizes marginalized or economically challenged populations. These principles have not been fully achieved yet, especially in the health care sector. To ensure equal access to orphan drugs for all rare diseases, an EU-wide procurement has been considered but this did not materialize. This may have improved vulnerable patients' affordability and accessibility to orphan drugs and in general, to expensive and innovative products in lower GDP European countries. This may have also contributed to lower prices through the procurement process. In reality, it is the author's experience that the net price is higher in lower GDP countries.

Because orphan drugs are dedicated to a small sample of the population by definition, they are marginally the target of EU policy makers. Agricultural workers, on the other hand, represent a sizable population in most countries, with an effective and vocal union organization leading large and impressive exhibitions in Brussels on a regular basis during budget discussions. Therefore, they represent a strong voting power and thus are more in the focus of policy makers. The low access to orphan drugs in some countries ultimately represents a denial of the EU foundation: solidarity and equity. It is time to take action and provide fair access to orphan drugs across the European Union.

REFERENCES

[1] Jonsson B, Hofmarcher T, Lindgren P, Wilking N. Comparator report on patient access to cancer medicines in Europe revisited. IHE Report 2016:4. IHE: Lund.

[2] Iyengar S, TayTeo K, Vogler S, et al. (2016) Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis. PLoS Med 13(5): e1002032. doi:10.1371/journal.pmed.1002032.

[3] Vogler S, Lepuschütz L, Schneider P, Stühlinger V. Study on enhanced cross-country

coordination in the area of pharmaceutical product pricing. European Commission, Directorate General

for Health and Food Safety Ed.; Brussels: Publications Office of the European Union 2015. Available at: https://ec.europa.eu/health/sites/health/files/systems_performance_assessment/docs/pharmaproductpricing_frep_en.pdf. [Accessed September 13, 2017].

[4] Carone G, Schwierz C, Xavier A. Cost-containment policies in public pharmaceutical spending in the EU. European Commission-European Economy. Economic papers 461 [updated September 2012]. Available from: http://ec.europa.eu/economy_finance/publications/economic_paper/2012/pdf/ecp_461_en.pdf

[5] Remuzat C, Urbinati D, Mzoughi O, et al. Overview of external reference pricing systems in Europe. J Mark Access Health Policy. 2015; 3: 10.3402/jmahp.v3.27675. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4802694/. [Accessed September 14, 2017].

[6] European Commission. Solidarity in Health: Reducing Health Inequalities in the EU. Available at: http://ec.europa.eu/health/social_determinants/policy/commission_communication_en. [Accessed September 14, 2017].

[7] Kenny, M. Crazy" European Orphan Drug Pricing System Has To End. SCRIP Pharma Intelligence Pink Sheet. 2016. Available at: https://pink.pharmamedtechbi.com/PS118869/Crazy-European-Orphan-Drug-Pricing-System-Has-To-End. [Accessed September 14, 2017].

[8] De Cock Jo. Differential Pricing of Medicines in Europe: Implications for Access, Innovation, and Affordability. ISPOR 19th Annual European Congress Plenary Session. October 2016. Vienna, Austria. Available at: https://www.ispor.org/Event/ReleasedPresentations/2016Vienna. [Accessed September 14, 2017].

[9] Towse A, Pistollato M, Mestre-Ferrandiz J, Khan Z, Kaura S, Garrison L (2015) European Union Pharmaceutical Markets: A Case for Differential Pricing?, International Journal of the Economics of Business, 22:2, 263-275.

[10] Remuzat C, Tavella F, Toumi M. Differential pricing for pharmaceuticals: overview of a widely debated pricing concept and key challenges. ISPOR 18th Annual European Congress. Milan, Italy. November, 2015. Available at: https://www.ispor.org/research_pdfs/51/pdffiles/PHP71.pdf. [Accessed September 14, 2017].

[11] Yadav, P. Differential Pricing for Pharmaceuticals. Study conducted for the U.K. Department for International Development. 2010.

[12] Young K, Soussi I, Toumi M. The Perverse Impact of External Reference Pricing (ERP): A Comparison of Orphan Drug Affordability in 12 European Countries. A Call for Policy Change. Journal of Market Access & Health Policy, 5:1, 1369817, DOI: 10.1080/20016689.2017.1369817

Q&A

Rare Diseases and the Patient: An Interview with Clark Paramore and Jennifer Helfer

Our editorial board member for *Value & Outcomes Spotlight* had the opportunity to sit down with Clark Paramore and Jennifer Helfer, members of the team at bluebird bio, to discuss severe, rare diseases and the impact specifically on patients. Their current research is focused on establishing the burden of disease for individuals living with transfusion-dependent β-thalassemia (TDT). This involves retrospective analysis of real-world data sources, as well as prospective studies that are utilizing innovative smartphone techniques to capture daily time impact and health-related quality of life data. All of their studies require strong input and collaboration with patient advocacy organizations and individuals living with TDT. The cumulative outputs from these studies will help clarify the value argument for an investigational, one-time gene therapy to treat TDT.

Value & Outcomes Spotlight: Please tell us a little about yourselves, and how you see your work impacting people living with rare disease?

Clark Paramore & Jennifer Helfer: Our current work revolves around developing potentially transformative gene therapies for severe genetic diseases and T cell-based immunotherapies for people with cancer. We work closely together to bring insights and disease expertise from people living with rare diseases into our value demonstration and evidence generation strategic plans. We believe that this approach will ultimately result in stronger, more credible evidence to illustrate to all stakeholders (ie, patients, providers and payers) the true impact of the disease being studied, and the potential value of new therapies coming to the market.

As one example of this approach, our work currently involves working with a team on conducting multi-country observational studies to establish the daily impact on individuals and caregivers living on transfusion-dependent β-thalassemia (TDT). Other members on the team include two individuals living with TDT. These individuals have helped shape the design of the study, informed the study protocol,

and guided the development of a smartphone app that will serve as a daily diary.

What are your thoughts on the current landscape of rare disease patient advocacy in the United States and in other parts of the world (if possible)?

A rare disease, sometimes referred to as an orphan disease, is any disease that affects a small percentage of the population. However rare diseases don't only affect the individual diagnosed, they also impact families, friends, and caregivers. As a whole, a global community of people facing similar issues has formed and has elevated the voice of people living with rare diseases in a way that it is no longer rare. Within this community many great groups and advocacy organizations are championing this voice, especially when it comes to informing policy decision making aimed at solving a health problem and improving quality of life.

It's clear that there is a positive trend in groups and advocacy organizations pushing for, and achieving, a greater patient voice in the HTA process in many countries. This only makes sense given people living with a disease are the stakeholder group that should benefit most from a credible, evidence-based decision making process. Our belief is that once the stories of these efforts are more widely known, other patient groups will become energized to become more engaged in future HTA assessments.

What are the challenges faced by organizations that advocate for individuals living with a rare disease? What are some of the positive developments? (Feel free to highlight the efforts of different countries or organizations)

Patient involvement in the HTA process is still generally in its infancy and very few HTA agencies currently involve and integrate patients' perspectives in their assessments. Of those HTA agencies that have included the patient perspective, there is an absence of a clear methodology and process on how and when to engage patients (eg, where is the patient perspective most needed or useful). Rare disease advocacy groups are already challenged by a lack of capacity and time to integrate patients into the HTA process, and the lack of a clear process only exacerbates this issue. The end result is that the patient perspective is missing from assessments and final reports.

Luckily there is increasing interest from both HTA agencies and patient groups to work together to increase the incorporation of the rare disease voice in the process of planning and decision making. Organizations in Europe such as the European Patients Forum, EUPATI, and EURORDIS have spearheaded many efforts to establish frameworks and guidances for patient involvement in HTA and provide training and mentorship to the community.

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What could help to drive forward the rare disease voice agenda around the world?

Building off the momentum currently within the rare disease community is key. There are a number of efforts that are important to drive forward optimal inclusion of the rare disease voice, including: 1) bringing together stakeholders to construct an understanding of the global HTA environment, as well as the nuances of individual country agencies; 2) working together to create detailed frameworks and processes for how and when the rare disease community can contribute actively in HTAs; and 3) creating assessable education and training programs, particularly at the country level.

How does research, particularly HTA and HEOR, feature in driving forward the agenda of rare disease patient voices? How can measurement of patient's quality of life using PRO instruments help us to understand the rare disease patient's perspective?

What becomes clear whenever we meet with individuals (and their families) living with a rare disease is that many feel they have had to live their journey 'on their own' and that others in society (eg, neighbors, coworkers, even clinicians) cannot understand what they deal with on a day-to-day basis. HEOR and associated HTA efforts can provide one type of outlet for these individuals to be able to tell their story and educate other members of society on the impact of their disease. HEOR can leverage research tools (eg, databases, PROs) that can generate a credible evidence base for what these individuals know they have been experiencing in living with the rare disease. In some situations these efforts can actually provide relief to individuals and families with rare diseases because they feel like their voices are finally being heard.

The FDA defines a PRO as a measurement based on a report that comes directly from the patient about the status of that patient's health condition ***without amendment or interpretation of the patient's response*** by a clinician or anyone else. In our view, this recognition of the importance of the patient's voice in describing the impact of their disease is even more relevant in rare diseases, as only a limited number of clinician key opinion leaders may be able to diagnose the condition, and may bring their own biases into describing the impact of the disease on those affected. Our own research, for example, has shown noticeable differences in what patients view as the most impactful symptoms of their disease, as compared to the views of their clinicians. As we continue to add additional patients with a rare disease into our PRO research efforts, we can feel more confident that we are evaluating the attributes of the disease that are most important to patients, and better assess the clinically meaningful impact of our therapies.

International Society for Pharmacoeconomics and Outcomes Research
505 Lawrence Square Blvd. South
Lawrenceville, NJ 08648 USA