

VALUE & OUTCOMES SPOTLIGHT

An ISPOR publication for the global HEOR community

Policy Changes From the 21ST CENTURY CURES ACT

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NOVEMBER/DECEMBER 2018
VOL. 4, NO. 6

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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.

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

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

Published bi-monthly by:
ISPOR

505 Lawrence Square Blvd. South
Lawrenceville, NJ 08648 USA
Tel: 609-586-4981; Toll Free: 1-800-992-0643
Fax: 609-586-4982; website: www.ispor.org

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

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

Direct photocopy permission and reprint
requests to Managing Editor.

© 2018 ISPOR—The professional society for health
economics and outcomes research.

While *Value & Outcomes Spotlight* is designed to provide accurate
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FROM THE EDITOR

The US Food & Drug Administration has just released its highly anticipated framework for their real-world evidence program, which they were called upon to develop by end of 2018 as part of the 21st Century Cures Act. Knowing the importance of this framework for RWE generation, we selected the Cures Act as our theme for this issue of *Value & Outcomes Spotlight*.

Our feature article points out that it is not just FDA that has demonstrated interest and made accommodations for RWE, but the European Medicines Agency and other regulatory bodies around the world that have done so. This is in response to the growing recognition of an “efficacy-effectiveness gap” in the way in which interventions perform in highly controlled trials versus real-world clinical practice. The proliferation of electronic health records and other forms of real-world data as well as advances in statistical methods and computing power are increasingly making evidence generation more timely and reliable. Regulatory authorities are in tune to this and seeking to make use of RWE for decision making, just as payers have done for the past two or three decades.

But evidentiary standards for regulatory decision making are high and one thing that’s clear from FDA’s RWE Framework is that there is no intention of relaxing these standards when it comes to product labeling. The real question is not necessarily whether regulatory authorities will accept RWE, but rather will they accept evidence from the non-randomized study designs that typify much of RWE generation. The one exception is the pragmatic clinical trial, the only real-world research design that does include randomization to treatment assignment, so there is some speculation that this will become favored by regulatory and more widely used in the future.

Our ISPOR Central section contains a wide variety of material of interest to the ISPOR membership, including HEOR news, an update from the editors of ISPOR’s highly successful flagship journal, *Value in Health*, individual and chapter awards, as well as reports and photo galleries from various ISPOR meetings, including our recently convened ISPOR Europe conference in Barcelona.

Finally, we include a memorial for ISPOR’s Founding Executive Director, Marilyn Dix Smith, whose passing we learned of this past October. It is impossible to overstate Marilyn’s influence on the field of HEOR through the creation of our Society. She is the one individual whose dedication of time, energy, and resources brought the organization to the success and prominence it has enjoyed for so many years. She will certainly be missed.

All of us here at *Value & Outcomes Spotlight* wish you the best for the holiday season and new year. See you in 2019!



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



ISPOR SPEAKS

Collaboration to Advance the Science: ISPOR's Institutional Council

Pamela B. Blumberg, MPH, DrPH, ISPOR Institutional Council Chair (2018)

It has been more than 25 years since I found my calling as a “droupie” or data groupie. What followed were positions where I utilized surveys, claims, electronic medical records, and other data to generate real-world evidence for the definition and optimization of illness burden, treatment patterns, healthcare outcomes, and costs following specific medical and pharmaceutical interventions. ISPOR has provided me with numerous learning and career opportunities through short courses, webinars, conference sessions, and networking. For the past 6 years I have had the privilege to give back, serving as a member of the ISPOR Institutional Council and for the last year, as Council Chair.

THE INSTITUTIONAL COUNCIL

The Council today comprises representatives from more than 30 biopharmaceutical, medical device, and service provider companies. Our mission remains to support ISPOR proactively as a scientific and educational society. This is accomplished by undertaking specific projects which promote the development of the field of health economics and outcomes research (HEOR) globally, the informed application and communication of HEOR results in healthcare decision making, and the enhancement of the quality of research by institutional members. In addition, the Council acts as an advisory body to the ISPOR board, providing a forward-looking perspective.

During this past year, we have had meetings of the full Council with invited speakers in Baltimore and Barcelona coinciding with the ISPOR 2018 and ISPOR Europe 2018 conferences, as well as regular teleconferences to provide ongoing activity updates and discuss new business. In addition, the Annual Strategic Meeting convened in August with our gold and platinum members to kick off new Council initiatives and identify topics and trends important to the future of both HEOR and ISPOR for further investigation.

DEFINING THE FIELD OF HEOR

The Council has led an ongoing effort in partnership with the ISPOR Faculty Advisor Council to develop and advance the ISPOR HEOR Competencies Framework™ (<https://www.ispor.org/strategic-initiatives/more/heor-competencies-framework>) and HEOR competencies inventory.™ The inventory contains 41 competencies mapped to 10 key competency domains and is currently targeted towards new graduates and young professionals.

10 Competency Domains

- Business Management
- Career Development
- Communication and Influence
- Drug Development
- Economic Methods
- Health-System and Payer Expertise
- HEOR Methods
- Observational Methods
- Patient-reported Outcomes and Patient Preference Methods
- Statistics and Modeling Methods



The results of an ISPOR member survey demonstrating both the importance and relevance of each competency to specific HEOR job types were presented in Barcelona at a round table discussion. The next phase of this initiative entails defining each competency in greater detail including key topics to be understood and mastered; identifying whether the competency is technical or strategic and how expertise is acquired; define how ISPOR and others can help members develop these competencies whether inside or outside the classroom; and determine which competencies are most critical to different job types.

FURTHERING THE DEVELOPMENT OF HEOR PROFESSIONALS

The Institutional Council is also collaborating with the Health Technology Assessment Council on updating the Global Health Systems Roadmap and developing Health System courses for all major global markets. Together this group is leading curriculum development for a new payer short course to be offered as a stand-alone course and as part of the global Health Systems courses at all future ISPOR international and regional conferences. At our meeting in Barcelona, Shelby Reed, past president of ISPOR, provided an overview of ISPOR's Women in HEOR initiative and its activities since the inaugural meeting in Glasgow. While the Competencies Inventory and Payer Short Course address some of the needs identified, additional common areas of interest and possible collaborations such as webinars, networking opportunities, and mentoring programs are elements the Council will continue to explore in the future. >

INCREASING ISPOR'S GLOBAL PRESENCE

During our Strategic Meeting with platinum and gold members of the Council, much of the discussion centered on where and how ISPOR as an organization could take the lead to increase HEOR awareness among our organizations' internal and external stakeholders and help prepare for the future by coalescing the problems, approaches, and appropriate tools of HEOR. By discussing important issues with ISPOR's top leadership and discussion makers, the Council is providing ideals and support to continue to advance the understanding and the use of HEOR to improve healthcare decisions.

2019 AND BEYOND

As 2018 and my tenure as Institutional Council Chair comes to a close, I find that rather than reflect on the many factors which changed the trajectories of both my personal and professional life this past year, I prefer to look forward to the opportunities and challenges ahead. These include learning what my new adoptive home state has to offer, collaborating with coworkers in my new role leading real-world evidence strategy, and further aiding ISPOR and the Institutional Council in increasing their reach to the global HEOR community and key stakeholders. ●

Additional Information

For more information on the ISPOR Institutional Council, go to <https://www.ispor.org/member-groups/councils-roundtables/isor-institutional-council>

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IN MEMORIAM

A Tribute to ISPOR Founding Executive Director Marilyn Dix Smith, RPh, PhD



We learned with great sadness, that Marilyn Dix Smith, who guided and shaped ISPOR for nearly 20 years as its Founding Executive Director, recently passed away. Her unexpected death is a loss for the health economics and outcomes research (HEOR) community and for her family, many friends, and colleagues.

ISPOR extends its deepest condolences to Marilyn's beloved husband Dr William F. McGhan. Bill was ISPOR's first president and, as you might expect, someone who Marilyn shared many of the same interests, including gardening and operating a vineyard in her native Ohio. Our sympathies extend to her

children, Brent Smith, Brian Smith, Matthew McGhan, and Monica Vandenberg; 8 grandchildren; and 2 sisters, Roberta Sullivan and Patricia Casillas.

Her career included serving in several executive roles at Lederle Laboratories, including director, managed care pharmacy, and director of quality control. Marilyn received her BS in pharmacy and PhD in pharmaceutical science from Ohio State University. She published many scientific articles and delivered many presentations over the years on HEOR-related topics. She was also a cofounder of the American Association for Pharmaceutical Scientists, a member of the American Society of Association Executives, and involved in many other pharmacy and healthcare professional organizations.

At ISPOR, Dr Smith's vision shaped our society into the leading global organization for HEOR. She led the Society through many milestones, including its first scientific conference on HEOR in 1996, the establishment our regional chapters, the launch of our flagship publication *Value in Health*, the creation of the Society's short course program, the founding of our student network, the organization of the global consortia and networks, and the development of books and many online HEOR resources.

For nearly 20 years Marilyn Dix Smith was the guiding force behind ISPOR's foundation, growth, and direction. She also recognized and greatly valued the contributions of its members and leaders. Upon her retirement in 2014, Marilyn requested that the Society establish an award to recognize outstanding volunteer leaders for their consistent, broad, and meaningful direction to ISPOR. The Marilyn Dix Smith Leadership Award was established that year in her honor.

With her vigor and passion, Marilyn inspired all who met her. She will be dearly missed and fondly remembered. While we grieve our loss, we are thankful for having our lives enriched by Marilyn's essence, kindness, ideals, and personal and professional contributions.

For those who would like to pay tribute or tell a story about Marilyn as the inspiring friend, colleague, and leader that she was, please go to www.ispor.org and post a comment on her remembrance page. ●

"Marilyn was a visionary, and took the organization from nothing to a huge multi national group. She had a vision as a leader, but most of all she was a dear sweet woman and a wonderful friend. I will miss her and I've missed seeing her at recent events, and offer all my best for Bill and her family."

Lorne Basskin, Friend and Colleague

"She was immensely helpful and supportive when I became the ISPOR Institutional Chair. Her guidance was much appreciated. RIP, Marilyn, I'm sure you will continue to organize those in the next life!"

Sissi Pham, ISPOR Institutional Chair

"It's with much sadness that I learned about Marilyn Dix Smith passing, ISPOR's Founding Executive Director. Marilyn was an inspirational figure when I just started my career and involvement with ISPOR. I will never forget her gentle guidance when we discussed the idea of establishing the ISPOR South Africa Chapter, the first in Africa. Her leadership, passion, and support during the process went way beyond what any Founder and CEO could do given the size and magnitude of ISPOR at the time!"

Joao Carapinha, Founder ISPOR South Africa Chapter



A Career Intertwined with ISPOR Leadership: Finn Børlum Kristensen

Finn Børlum Kristensen, PhD, MD, ISPOR's 2018 Marilyn Dix Smith Leadership Award recipient, is highly active in the organization. If you search for his name on the society's website you will come up with a slew of results. Dr Kristensen has presented at ISPOR events around the world on subjects such as good research practices in health technology assessment (HTA), including the ISPOR HTA Council, roundtables, and HTA Training Program. He was elected to and served on the ISPOR Board of Directors from 2011 to 2013 and has chaired the ISPOR HTA Council since 2013.

Being named the 2018 Marilyn Dix Smith Award recipient made Dr Kristensen "Genuinely really happy, because it is an appreciation of work that has gone on for more than 10 years—it was completely unexpected and just a joy. This award was given late in my career and it helps me see that I have made a difference, which is great!"

Receiving this award also gave him an opportunity to address the participants during the plenary at ISPOR's annual meeting in May 2018. "I had some thoughts about the future of ISPOR that I wanted to share; that was an added value, you could say," Dr Kristensen tells *Values & Outcomes Spotlight*. "It forced me to think about the current and future status of ISPOR."

DEEP INVOLVEMENT IN DEVELOPING HTA IN EUROPE

Looking at Dr Kristensen's career, it is no wonder that he naturally gravitated to ISPOR's mission of helping produce better health outcomes. As a practicing primary care physician in Denmark, Dr Kristensen says he increasingly became interested in epidemiology. "Epidemiology feeds into what ISPOR is doing because ISPOR is the society for outcomes research, and outcomes research is about statistics and population health data," he explains.

His first foray into outcomes research was a study based on the Danish Medical Birth Register, a national register that has been in existence in Denmark since the 1960s and gathers information from pregnant women's prenatal care visits, birth, and the newborn delivery. This led to his PhD, and after a stint in academia as a postgrad, in 1997 he joined the Danish Health Authority to become the first head of the Danish Centre for HTA (DACEHTA), a position he held until 2009.

During that time, he was also working with the Ministry of Health on some European Commission matters, in the field of cross-



border patient services. According to Dr Kristensen, that eventually led to a proposal that formed the European Network for Health Technology Assessment (EUnetHTA) in 2016. He was chairman of the EUnetHTA Executive Committee until 2006. "If you were to talk about my career arc, it was probably the top of the arc, because it was a fantastic tour with all these different institutions and different researcher backgrounds, moving forward with collaboration in this field of HTA," Dr Kristensen says.

Additionally, Dr Kristensen has been a professor in Health Services Research and HTA at Faculty of Health Sciences, at the University of Southern Denmark since 1999, and currently is an independent consultant.

As an independent consultant, Dr Kristensen's goal is to help different stakeholders in HTA and outcomes research, including government

institutions and private medical device and pharmaceutical companies. "I'm in the same ballpark, but now I am independent and can help and provide my experience to facilitate knowledge and development," he says. "So of course, I would like to see some results from that in the coming years."

ADVANCING OUTCOMES RESEARCH AND ISPOR

Dr Kristensen's PhD in epidemiology—which is at the center of outcomes research—led to his work with HTA, and he believes that finding an accord between outcomes researchers and clinical researchers is easier now than a few decades ago.

"During the late 1980s into the 1990s, I would say that there were real clashes between the outcomes researchers and the trialists—the trialists being the people that were underlining that we really need randomized controlled trials to know about whether something works or not, and to the extent that it works. If we do not have control groups, randomize, and use blinding, we are at risk of bias, unknown influencing factors that play a bigger role than what we expect in our study with the data that we have," Dr Kristensen states. "I tended to agree a lot with the people on the trialist side, but on the other hand, you cannot run trials for everything."

Dr Kristensen attributes a lot of the advances in health outcomes research, and the more positive light in which it is now received,

to ISPOR's activities. "ISPOR has contributed to building respect towards outcomes research, because ISPOR members are doing a lot to develop good practices and making sure that sound methodology is applied," he says.

ISPOR is "Not just an organization for advocacy of outcomes research itself, it is an organization that is also improving methodology and helping people be critical about the interpretation of data," he explains.

Dr Kristensen sees an increasing role for ISPOR as data collection and data processing in the health outcomes field become more powerful. "This is a big opportunity for outcomes research, but it needs to be done with a lot of critical approaches in terms of methodology," he says. "Teaching that [methodology] and further developing it is a great task and ISPOR is positioned to do so."

In an interesting twist that was perhaps foreshadowing the future, Dr Kristensen's involvement with ISPOR began with a meeting in Copenhagen in 2007 with Marilyn Dix Smith as well as Michael Drummond, who was president of the Society at that time. Dix Smith and Drummond wanted to make EUnetHTA aware of the existence of ISPOR.

"It may be very dry to work with your studies and your textbooks and different kinds of exams and theses, etc, but being involved in ISPOR brings you closer to answering 'How can this be applied and actually make a difference in some way?'"
Dr Kristensen adds.

It did not take Dr Kristensen long to see the advantages of working with the Society. "I immediately saw the potential in ISPOR as a Society that can enable collaboration, where people can put in work to make a difference," he says. "It already had a substantial secretariat and good people working there who could facilitate."

Within a year or two of joining ISPOR, Dr Kristensen had helped establish the HTA Roundtables, first in Europe and then in North America, and then later in Asia, Latin America, and recently Middle East and Africa. "And of course, that could only happen because there was this collaboration with the people at ISPOR," he adds.

In particular, Dr Kristensen singles out ISPOR's Nadia Naaman, Senior Director, Scientific & Health Policy Initiatives, as one of the people he has worked with fruitfully. "She and I have had a wonderful collaboration over the years," he says.

Even though Dr Kristensen was still leading DACEHTA and EUnetHTA at the time he joined ISPOR, he welcomed what the Society did and continues to do.

"I saw that by doing some work within ISPOR, I could see things moving ahead where there was a common agenda between ISPOR and myself," he explains. "It was good for ISPOR and it was good for me because I wanted to see HTA better implemented and understood. It is a good thing to have this research-based policy development, advising and informing decision makers based on research."

TO FUTURE HEOR AND HTA RESEARCHERS: JOIN ISPOR

As someone who has found great value in ISPOR's programs, Dr Kristensen suggested in his award address that future researchers in the health economics and outcomes research field should consider doing some voluntary work for the organization and see if there is an opportunity to join a chapter or facilitate task forces or special interest groups. That way when students finish their studies, "they will be hitting the ground running," he explains.

ISPOR can give students a way to apply their research in a real-world way. "It may be very dry to work with your studies and your textbooks and different kinds of exams and theses, etc, but being involved in ISPOR brings you closer to answering 'How can this be applied and actually make a difference in some way?'" Dr Kristensen adds.

And ISPOR's value extends beyond school, he emphasized. Once students are finished with school and are starting their professional career, "They should pay attention to opportunities provided by ISPOR," Dr Kristensen says. "They should try to get into an HTA institution, academic group, or consultancy that works on HTA processes and get to know what it is about. From that point, they can then decide if they want to go work at the HTA institution, or if they would like to work with consultancies that are feeding into submissions and different kinds of things in these processes or go work in the industry with this knowledge and approach."

Whether they choose to work with government institutions, private companies, or consultancies, students will be applying the same approaches to look at evidence and data in their day to day work. Students may find that the perspectives may differ between each of these stakeholders—while national institutions are interested in costs related to outcomes, private companies are interested in bringing their products to the market in a favorable way. But these companies also "Know the game of providing evidence, and knowing the game is what I recommend to young professionals," Dr Kristensen says.

And if a student is strictly into research, they can still have a viable HEOR/HTA career, Dr Kristensen states, "If you are really into primary research and are really one of those who can stay with the same problem and analyze it from different angles for years, maybe tens of years, then you should stay with primary research. We really need those primary researchers." He continues, "I myself, I could not stay at my desk sufficiently long enough to go on analyzing the same problem, but for those people who can do so, I have the highest respect. Many other people are more lateral, they are more interested in how something can be applied. Those people can also enjoy the HTA field."

Even though he is no longer with EUnetHTA and is an independent consultant who enjoys being able to spend more time with his family (at the time of this interview his ninth grandchild was on the way), Dr Kristensen will continue his volunteer work with ISPOR. "I will definitely still be involved in ISPOR activities and see how opportunities emerge for continuous involvement, because it is a great Society and it has provided me with so many friends, colleagues, and contacts whom I really appreciate," he explains. ●



New ISPOR Program Recognizes Outstanding Contribution of Regional Chapters: Spotlight on Russia St. Petersburg, Mexico, and Colombia Chapters

Value & Outcomes Spotlight had the opportunity to talk to the presidents of the ISPOR Regional Chapters that received the ISPOR Outstanding Chapter Award and ask them to reflect on the chapter's significance, possible impact, and contribution to the development of the health economics and outcomes research (HEOR) supporting better health decision making in their countries.

The ISPOR Outstanding Chapter Award was established in 2017 to recognize the exceptional contribution and leadership of ISPOR Regional Chapters in advancing the ISPOR mission in ISPOR global regions Asia, Latin America, Europe, Middle East, and Africa. The award is offered in 3 categories based on chapter membership size: small, medium, large. ISPOR staff assesses the chapter's contributions by applying eligibility and selection criteria in their review of the information available from the Chapter Annual Reports, chapter input to ISPOR publications, and ISPOR activities throughout the year.

Value & Outcomes Spotlight: Congratulations on receiving the 2018 ISPOR Outstanding Chapter Award. For many ISPOR Regional Chapters' members, engagement and contribution are among the key challenges that prevent them from reaching their full potential. How do your chapters connect with members in your regions and create a collaborative environment?



Alexey Kolbin, MD, PhD, President, ISPOR Russia St. Petersburg Chapter, St. Petersburg State University, St. Petersburg, Russia. Scientific communication between Chapter members is based on historical ties. In fact, that early collaboration

was one of the reasons for the Chapter's foundation. In the early 2000s, a few doctors and pharmacists from St. Petersburg State University and State Chemical Pharmaceutical Academy—experts in pharmacoeconomics—established a collaborative network to which they later invited mathematicians and healthcare managers. Thus, the connections between the Chapter members derive from strong academic scientific teamwork that has been developing for over 15 years. ISPOR Chapter status has given us an opportunity to make all our team activities more visible. The existing collaborative environment makes health technology assessment (HTA) projects a part of our daily work and provides a faster integration of new Chapter members.



César Alberto Cruz Santiago, MD, PHD, President, ISPOR Mexico Chapter, PEMEX, Mexico City, Mexico. Inside the ISPOR Mexico Chapter, our priority is to serve the members because the members are the most important part of the chapter.

That is why we work to plan activities, sessions, and products that offer value to our members. We organize academic sessions with topics of interest in HTA, pharmacoeconomics, health policies, etc. We also organize an annual 3-day event, with an excellent group of national and international speakers, and of course, distinguished members of ISPOR international, and at least one other additional intermediate event to complement our activities. In the past year, we organized a multiple criteria decision analysis (MCDA) course with the participation of international ISPOR members and the first official TreeAge Training in México. These activities are planned with the chapter members in mind, and their opinions are taken into consideration when we generate these events. We give them the

opportunity to engage and interact with the various decision makers both in the academic area and public and private sectors to build topics of interest and create the possibility of making decisions together.



Camilo Ernesto Castañeda Cordona, MD, President, ISPOR Colombia Chapter, NeuroEconomiX, Bogota, Colombia. Our chapter continuously inquires about the interests and needs of the chapter members and the stakeholders in the health system. This

guarantees that our activities are aligned with the needs of our members and keeps them feeling connected with the chapter. Likewise, it makes the members value and attend our events. Thanks to this, we have managed to raise awareness of health economics and outcomes research (HEOR) in our country and positively impact our health system. The health economy science in Colombia has had an important growth in the past 15 years, which has materialized with the creation of the health technology agency (IETS) that recently turned 5 years old. Health economics in Colombia is so important that it is a tool used not only by the health technology agency but also by the health ministry, payers, and providers as an intelligent decision-making tool.

We are proud to say that ISPOR Colombia Chapter has contributed to this evolution, promoting knowledge and generating academic spaces to spread this information. The chapter offers congresses, workshops, and symposia to people from government, academia, and payers. The stakeholders have learned pharmacoeconomics and to use these tools through the programs we offer, specifically the cost-effectiveness studies. Today, we are a leading country in Latin America and a pioneer in the use of these economic tools for decision making and we look forward to the continuation of HEOR growth in the region.

Your chapters have been recognized for developing and successfully implementing an outstanding program of activities in the areas of education, research, and publication. Can you describe how ISPOR as an organization has contributed to this recognition?

AK: I would like to mention again the history of ISPOR in Russia. Since 1998, when the first chapter was opened in Moscow, Russia (president Pavel Vorobiev), the scientists have been studying the

methodology of pharmacoeconomics, pharmacoepidemiology, and outcomes research. The establishing of Russia HTA Chapter (president Vitaly Omelyanovsky) in 2011 in Moscow and the St. Petersburg Chapter in 2012 made the ISPOR methodology of conducting HEOR studies the leading one in the country. Gradually, public health managers and decision makers have been involved in HTA processes. ISPOR provides access to methodological tools and guidelines, starting from scientific journals to educational webinars. They present great importance to us and serve as the foundation for organizing and presenting our educational courses and conducting scientific research, which are accepted at not only the regional, but also the national levels.

CACS: ISPOR as an organization has participated as a bridge that unites, in a clear way, the different stakeholders of the health sector. This allows, in an impartial way, the collaboration and joint work of all the key organizations involved. It also provides scientific information for good practices in health economics and in the evaluation of health technology. For instance, when ISPOR participated in the update for the national guide for the realization of HTA and the national guide for the evaluation of medical devices, these actions were carried out with the ministry of health. As an academic organization, ISPOR has the possibility of integrating collegiate organizations for the realization of common projects, the generation of research works involving 2 or more members of the health sector and allows participation in the achievement of commitments that require the conjunction of the parties by being the element that allows the joint decision making.

CC: Mainly because our chapter has made a huge effort to have in its team a combination of key stakeholders, including from academia. These members not only come from the best universities in the country but also from the most technical entities of the government. By attracting these types of affiliates, a favorable and fruitful environment for education, research, and scientific publications is generated. ISPOR, as the leading society of HEOR, has contributed because it offers high-quality academic programs and educational activities that are programmed every year worldwide through its conferences. ISPOR Colombia Chapter members take advantage of the tools that ISPOR offers to keep updated on the latest trends of HEOR and the opportunities that the society offers to share knowledge and, in this way, contribute to the growth of health economics and outcomes research in our country.

Looking at your chapters' achievements this past year the HEOR field in your regions this past year, what are you most proud of and what goals do you have for the next year in fulfilling your chapters' mission?

AK: It seems to us that our main achievement is that we as a chapter have managed to bring together the most experienced specialists in the field of pharmacoeconomics and HTA in St. Petersburg, which is a city with a population of 5 million and huge scientific potential. Moreover, these are people from different academic schools and universities. All of them are now conducting research in the field of HTA using the same ISPOR methodology, which is extremely important. These are the people with whom we are presently preparing a handbook for conducting pharmacoeconomic studies using mainly ISPOR methodology and guidelines. Completion of this book by next year is our ambitious challenge. In addition, I would like to draw your attention to the fact that we have developed and

approved from the Russian Ministry of Health a 1-week educational course titled "Current Topics in HTA," with attendees receiving continuing medical education (CME) credits at the end of it. Both maintenance and improvement of this course are among our main goals for the coming year.

CACS: In the past year, we have increased the number of members. In 2016, there were approximately 110 associates; we currently have more than 300 and we expect that for the annual meeting in 2020, we will welcome more than 500 members. We have been able to hold monthly educational and informational sessions at no cost to our members. Our goal is that for the next year we will continue holding these meetings and providing our members the opportunity to learn from international experts in HEOR, offering our members the possibility to stay up to date in their knowledge. The chapter is proud to say that we have promoted the collaboration between ISPOR, industry, and government to make possible the creation of the Mexican quality-adjusted life years (QALYs). We already have the authorization of EuroQol, and we will start in the first quarter of 2019 with a study to continue with the development of this project. We would also like to continue with academic events and increase our participation in the generation of knowledge from the development of original research and contribute to the dissemination of it. We would also like to proceed with the formalization of our student chapter. We understand the importance of new professionals and students in continuing to be a leading chapter.

CC: One of the activities that we are most proud of is the success of our ISPOR Colombian Chapter conference this year, where we exceeded attendance expectations, had world-class speakers, and brought together the main players of our health system to discuss the most important issues in the field. Additionally, we are very proud to be the venue for the next ISPOR Latin America conference. Next year, we will have the Latin American conference in Bogotá—ISPOR Latin America 2019! The conference will include excellent sessions, workshops, webinars, and other educational activities, and the ISPOR Colombia Chapter is planning on collaborating greatly with the development of this important conference. This will be one of our main goals for next year. By having the opportunity to host the ISPOR conference in Colombia, we will strongly encourage our members to take advantage of this opportunity, and we hope to provide a fruitful experience that will satisfy the increasingly educated and demanding public. For the next year, we also want to make big contributions to the health economy, reaching a larger number of people in both the government and industry and making our chapter an increasingly larger group that seeks to contribute to the welfare of the entire Latin America region.

About ISPOR Regional Chapters

As the field of HEOR has grown in importance, ISPOR's global HEOR community has expanded to more than 20,000 individual and chapter members from 120+ countries worldwide. ISPOR Regional Chapters facilitate the global flow of information related to healthcare decision making. There are currently 86 ISPOR Regional Chapters in global regions.

For more information, go to www.ispor.org/member-groups/global-groups.



Call for Nominations

The ISPOR Awards Program is designed to foster and recognize excellence and outstanding technical achievement in pharmacoeconomics and outcomes research. These awards will be presented at ISPOR 2019, May 18-22, 2019, New Orleans, LA, USA.

The ISPOR Avedis Donabedian Outcomes Research Lifetime Achievement Award | **Nominations due by February 8, 2019**

The ISPOR Avedis Donabedian Outcomes Research Lifetime Achievement Award was established in honor of the late Avedis Donabedian MD, MPH to acknowledge those individuals who have made a major contribution to the improvement of health outcomes. Nominations may be made by any ISPOR member. Members may nominate more than one person; however a completed letter of recommendation must accompany each nomination.

For complete details on background, criteria, selection process, and nature of the award, see: <https://tinyurl.com/yba48czc>.

ISPOR Marilyn Dix Smith Leadership Award | **Nominations due by February 8, 2019**

The Marilyn Dix Smith Leadership Award recognizes an individual who has shown consistent, broad, and meaningful direction to the Society in a leadership role. Nominations for the Marilyn Dix Smith Leadership Award require a letter of recommendation for the nominee, nominee's leadership contributions to the Society and nominee's CV.

For complete background, criteria, selection process, and nature of the award, see: <https://tinyurl.com/y7hm6pak>.

ISPOR Bernie O'Brien New Investigator Award | **Nominations due by February 8, 2019**

The ISPOR Bernie O'Brien New Investigator Award was established in 2004 to honor the long-standing commitment of Bernie J. O'Brien, PhD to training and mentoring new scientists in the fields of outcomes research and pharmacoeconomics. All nominations must include a letter of support for the nominee and a current edition of the nominee's CV essay indicating the reason for your nomination.

For complete background, criteria, selection process, and nature of the award, see: <https://tinyurl.com/ybh7zjmd>.

ISPOR Award for Excellence in Methodology and Application in Pharmacoeconomics and Health Outcomes Research ISPOR **Nominations due by February 8, 2019**

The ISPOR Award for Excellence in Methodology and Application in Pharmacoeconomics and Health Outcomes Research were established in 1997 to recognize outstanding research in the field of pharmacoeconomics and outcomes research methodology and outstanding practical application of pharmacoeconomics and outcomes research in health care decision making. Only ISPOR members may submit nominations (either their own publications or others). All nominations must include a brief cover letter indicating the reason for the nomination. Supporting documentation MUST include a PDF of the nominated paper.

For complete background, criteria, selection process, and nature of the award, see: <https://tinyurl.com/y9mdxa3> and <https://tinyurl.com/yb5s7f8y>.

Nominations should be sent to: awards@ispor.org

HEOR NEWS

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

1 New CMS Pay Model Targets Soaring Drug Prices (Modern Healthcare)

The Trump administration has accelerated its efforts to bring prescription drug costs under control, announcing the first mandatory Centers for Medicare & Medicaid Services (CMS) pay model. Speaking at the Hubert H. Humphrey Building, President Donald Trump introduced an aggressive proposal from Health and Human Services (HHS) to drive down prescription drug rates paid by Medicare Part B by indexing them to the much lower prices paid by other advanced countries and changing the way physicians are paid for administering those drugs.

<https://www.modernhealthcare.com/article/20181025/NEWS/181029944>

2 AbbVie's CLL Drug Venclxyto Too Expensive for NHS, Says NICE (pharmaphorum)

NICE has said AbbVie's Venclxyto (venetoclax), in combination with development partner Roche's MabThera/Rituxan (rituximab), is not a cost-effective use of NHS resources as a treatment for a kind of leukemia. The cost-effectiveness body said in first draft guidance that the combination should not receive regular NHS funding in relapsed or refractory chronic lymphocytic leukemia (CLL) in adults.

<https://pharmaphorum.com/news/abbvies-ctl-drug-venclxyto-too-expensive-for-nhs-says-nice/>

3 Minnesota Becomes First State to Sue Major Insulin Makers Over Price Gouging (Pharmalot)

In the latest sign of anger over the cost of insulin, the Minnesota attorney general on Tuesday filed a lawsuit accusing the three largest manufacturers — Eli Lilly, Sanofi and Novo Nordisk — with deceptively raising prices, the first state to go to court over the issue.

<https://www.statnews.com/pharmalot/2018/10/16/minnesota-sues-insulin-makers/?fbclid=IwAR2SJVCEhwzfyS1ygS7eXiBIAupJxrUV6KGP13INA2DrkSHieEOuApu0FE>

4 Huge Variations Between Countries in Time for Reimbursement Decisions on New Cancer Drugs (EurekaAlert!)

Some European countries take more than twice as long as others to reach health technology assessment (HTA) decisions to reimburse new cancer drugs following their approval by the European Medicines Agency (EMA). The average decision time is longer than one year in some countries, according to a study reported at ESMO 2018 Congress.

https://www.eurekaalert.org/pub_releases/2018-10/esfm-hvb101818.php

5 Pfizer CEO Says Company to Return to Drug Price Increases "as Normal" Starting in January, Despite Pressure from Trump (FirstWord Pharma)

Pfizer CEO Ian Read said during the company's third-quarter earnings call that it will likely go back to "business as normal" for drug price increases at the start of next year. In July, Pfizer rolled back on planned price hikes for certain drugs after US President Donald Trump had taken aim at the company and others for raising prices on their prescription products.

<https://m.firstwordpharma.com/pfizer-ceo-says-company-return-drug-price-increases-normal-starting-january-despite-pressure-trump>

6 Amgen Cuts Price of Cholesterol Drug Repatha (PharmaLive)

Amgen Inc, looking to boost use of its potent cholesterol drug Repatha, has cut the medication's US list price by 60% to \$5,850, the US biotechnology company said in October. Repatha and rival drug Praluent from partners Regeneron Pharmaceuticals Inc and Sanofi SA were launched in 2015 at list prices of more than \$14,000 a year. Sales of both — members of a class known as PCSK9 inhibitors that dramatically lower bad LDL cholesterol — have been constrained by onerous roadblocks to patient access by insurers looking to limit spending on the expensive drugs. Amgen's move "is clearly focused on helping patients afford the medicine at the pharmacy counter," said Murdo Gordon, the company's head of commercial operations.

<https://www.pharmalife.com/amgen-cuts-price-of-cholesterol-drug-repatha-by-60-percent/>

7 FDA Clears the First Consumer Genetic Test for How Well your Medications May Work — With Caveats (STATNews)

The US Food and Drug Administration has cleared the first DNA test meant to be marketed directly to consumers to help them determine how well certain drugs may work for them. The test was developed by 23andMe and, as with other tests from the consumer genetics giant, customers will be able to simply mail in a saliva sample to get results.

<https://www.statnews.com/2018/10/31/fda-clears-23-and-me-genetics-test-drug-effectiveness/>



ISPOR Conferences: **Contribute to Advance the Science!**



ISPOR 2019
 May 18-22, 2019
 Ernest N. Morial
 Convention Center
 New Orleans, LA, USA

Call for Abstracts

Abstract Submission Deadline: January 16, 2019

Notification Date: March 1, 2019

Early Registration Deadline: April 9, 2019



ISPOR Latin America 2019
 12-14 September 2019
 Convention Center
 Bogotá, Colombia
*Data & Value in Healthcare:
 2020 & Beyond*

Call for Abstracts

Abstract Submission Deadline: 13 March 2019

Notification Date: 1 May, 2019

Early Registration Deadline: 30 July, 2019

Submit your HEOR research, issue panel proposal, or workshop proposal to present at a 2019 ISPOR conference today! www.ispor.org



ISPOR Warsaw 2019

27-29 March 2019
 Warsaw, Poland



ISPOR Summit

October 2019
 Washington, DC, USA



ISPOR Europe 2019

2-6 November 2019
 Copenhagen, Denmark

Looking ahead to 2020...

ISPOR 2020

Orlando, FL, USA

ISPOR Europe 2020

Milan, Italy

ISPOR Asia Pacific 2020

Seoul, South Korea

For more information and registration: www.ispor.org

CONFERENCES & EDUCATION



Photo Highlights from 2018 ISPOR Conferences

The complete photo galleries and released presentations are online at www.ispor.org

ISPOR 2018

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

May 19-23 | Baltimore, MD, USA

3700+ Delegates

70 Countries Represented

ISPOR Asia Pacific 2018

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

8-11 September | Tokyo, Japan

1600+ Delegates

66 Countries Represented

~28%
increase
from 2016
Event

ISPOR Dubai 2018

Healthcare Decision Making in the Middle East and North Africa: Role of HEOR and HTA

19-20 September | Dubai, United Arab Emirates

400+ Delegates

38 Countries Represented

ISPOR Summit 2018

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

October 19 | Washington DC, USA

175+ Delegates Registered

ISPOR Europe 2018

New Perspectives for Improving 21st Century Health Systems

10-14 November 2018 | Barcelona, Spain

5500+ Delegates

93 Countries represented

Highest
attendance
at an ISPOR
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CONFERENCES & EDUCATION



ISPOR thanks our 2018 exhibitors and sponsors for your continued support. We look forward to working together in 2019.

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Accession	eMAX Health Systems	Lightspeed Health	RealHealthData
Adelphi	Envision Pharma Ltd	MA Provider	Remap Consulting
Amaris	European Market Access Network	MAESTRO Database	RTI Health Solutions
AMICULUM	Evalueserve	MAP BioPharma Ltd.	RWS Life Sciences
AMPLEXOR	Evid Science	MAPES	SchHarr, University of Sheffield
Analysis Group	Evidence Partners Inc.	Mapi Research Trust	Sciformix Corporation
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AplusA Real World	Exponent	MarksMan Healthcare Solutions	SIRIUS Market Access
Barrington James	FACIT.org/FACITtrans	McKesson Specialty Health	STATinMED Research
BaseCase	FIECON	Medical Data Vision Co. Ltd.	stève consultants
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Black Swan Analysis	Gareth Lee (G&J Lee Recruitment)	Merck	Talentmark
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BresMed	GfK	MS in Regulatory Science Program	The American Journal of Managed Care
Bristol-Myers Squibb	Gilead Science	Mtech Access	The CPRH Exam
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Clinical Practice Research Datalink (CPRD)	IBM Watson Health	Numerus	Univ. of Maryland
Clinical Study Support, Inc.	ICON	OKRA Technologies	Valid Insight
Clinical Survey Outcomes	IGES Group	OM1	Vienna School of Clinical Research
Cogvio / Value Outcomes	IMPAQ International	OPEN Health	Virtual Cockpit
Complete HEOR Solutions (CHEORS)	Ingress Health	Optum	Vitaccess
Cornerstone Research Group Inc.	InSite	OXON EPIDEMIOLOGY	Wickenstones
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Costello Medical Singapore Pte Ltd	Intexo Srl	Pharmatelligence	WIRB-Copernicus Group
Covance	Ipsos Healthcare	Pharmerit International	Worldwide Clinical Trials
CRA, Charles River Associates	IQVIA	PHARMO	Xavier University
Creativ-Ceutical	Janssen - GCC	PHMR	Xcenda
CRECON MEDICAL ASSESSMENT	Jefferson College of Population Health	Plamed Asia	York Health Economics Consortium
Crystallise Ltd	JMDC Inc.	Policy Analysis Inc. (PAI)	ZRx Outcomes Research Inc.
CTI Clinical Trial and Consulting Services	Johns Hopkins Bloomberg School of Public Health	PRA Health Sciences	ZS
CVS Health	Kantar Health	Precision for Value/Precision Xtract	
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		Prioritis Ltd	
		PRMA Consulting	



Measuring Value and Its Impact on Pricing and Coverage Decisions: ISPOR Summit 2018



Through content-specific scientific presentations and input from a broad mix of key stakeholders, these Summits provide ISPOR members with a valuable deep dive into areas of significant interest and importance to our Society. This ISPOR Summit was the third annual meeting held in Washington DC in the fall to focus on a specific topic that combined research and policy considerations.



On October 19, 2018, ISPOR hosted its third annual Summit in Washington DC. Building on the recently published work of ISPOR’s Special Task Force on US Value Assessment Frameworks, this year’s event focused on “New Approaches to Value Assessment: Towards More Informed Pricing in Healthcare.”

ISPOR convened a diverse mix of healthcare stakeholders to discuss the latest approaches in adapting health economic analysis to better reflect the value patients place on various healthcare services. Attendees gathered to continue to discuss and debate the current state of healthcare value assessment and its role in pricing and coverage decisions. Speakers presented practical steps to improve value measurement, highlighting such issues as the importance of developing approaches that better reflect patient and societal perspectives.

ISPOR CEO and Executive Director Nancy Berg opened the Summit by welcoming more than 180 attendees from regulatory, industry, academic, and patient interest group organizations. She then introduced the keynote speaker, former US Food and Drug Administration Commissioner Mark McClellan, MD, PhD, now at the Duke-Margolis Center for Health Policy, Durham, NC.

Dr McClellan spoke to the increasing relevance of healthcare value assessment, providing his perspective on current policy and practice issues surrounding value-based pricing for drug and other healthcare services. He highlighted the trends, opportunities, and obstacles within the field, stressing the important role value assessment can play in coverage and pricing decisions. He concluded his talk by presenting his thoughts on potential elements for the next generation of value assessment frameworks. ISPOR president Federico Augustovski, MD, MSc, PhD of the Institute for Clinical Effectiveness and Health Policy, Buenos Aires, Argentina moderated the question and answer session, during which Dr McClellan responded to inquiries surrounding the evolving nature of value assessments, noting the importance of incremental steps to ensure fundamental progress.

Five plenary sessions followed the keynote address, covering the current approaches, novel approaches, and possible future approaches to value assessment frameworks and pricing. These 5 sessions included:

- Current Value Frameworks: What’s New?
- Novel Approaches to Value Assessment Within the Cost-Effectiveness Framework
- Novel Approaches to Value Assessment Beyond the Cost-Effectiveness Framework

- Specific Value Assessment Considerations
- Practical Next Steps in Improving Value Measurement and Use

The first plenary session, “Current Value Frameworks: What’s New?,” focused on recent developments in value assessment, such as incorporating patient and societal perspectives into a broader value framework, the challenges in valuing potential cures, applications within cancer therapy assessments, and value-based contracting. This session was moderated by ISPOR Chief Science Officer Richard Willke, PhD. Speakers included Rick Chapman, PhD, Institute for Clinical and Economics Research, Boston, MA; Josh Seidman PhD, MHS, Avalere Health, Washington, DC; Lowell Schnipper, MD, Harvard Medical School, Boston MA; and Patrick Gleason, PharmD, Prime Therapeutics, Eagan, MN.

The second plenary session, “Novel Approaches to Value Assessment Within the Cost-Effectiveness Framework,” focused on the need to augment conventional cost-effectiveness analysis (CEA) to incorporate the patient perspective so as to capture a more complete view of the full value of various healthcare interventions. Speakers presented their positions on possible CEA modifications, including extending the scope of patient-reported outcomes and quality-adjusted life years (QALYs) to capture outcomes not conventionally considered, the need to acknowledge patient diversity, novel and potentially relevant concepts of value, and the use of distributional CEA to reduce inequality in health. Lou Garrison, PhD, University of Washington, Seattle WA, moderated the session. Speakers included Susan Griffin, PhD, University of York, UK; Nancy Devlin, PhD, Office of Health Economics, London, UK; and Jeroen Jansen, PhD, Innovation and Value Initiative, Los Angeles, CA.

The afternoon sessions expanded upon the morning’s CEA session to examine “Novel Approaches to Value Assessment Beyond Cost-Effectiveness Framework.” This session presented alternative approaches to value assessment that could be used to support healthcare decision making and pricing determinations. Speakers covered recent developments in the application of multiple criteria decision analysis, patient preference measures, and the limits of QALY measures of benefit, stressing that although some value frameworks may not be ready for prime time, they are currently being used to determine patient access to services. Shelby D. Reed, PhD, of Duke University, Durham NC moderated this session. Speakers included Robert W. Dubois, MD, PhD, National Pharmaceutical Council, Washington, DC; Charles E. Phelps, PhD, University of Rochester, Rochester, NY; J. Jaime Caro, PhD, MDCM, McGill University, Montreal, Canada; and F. Reed Johnson, PhD, Duke University, Durham, NC.

The next session, “Specific Value Assessment Considerations,” focused on value measures appropriate for specific decision and pricing contexts. Speakers presented their views on indication-based pricing, valuation of medical devices, and affordability as an expanded measure of value. This session featured presentations by Patricia Danzon, PhD, University of Pennsylvania, Philadelphia, PA; Liz Spurgin, MBA, Medical Device Innovation Consortium, Washington, DC; and Adrian Towse, MA, Office of Health Economics, London UK. Sachin Kamal-Bahl, PhD, Pfizer, New York, NY, moderated this session.

The final session provided an opportunity for Summit participants to reflect on and synthesize the learnings for the day’s sessions with the help of a multistakeholder panel. This session, “Practical Next Steps in Improving Value Measurement and Use,” was moderated by Dan Ollendorf, PhD, Tufts Medical Center in Boston. Joining Dr Ollendorf were 4 speakers representing industry interests, payer perspectives, and patient views: Newell McElwee, PharmD, MSPH, Boehringer-Ingelheim, Ridgefield CT; Suzanne Schrandt, JD, Arthritis Foundation, Washington DC; Patrick Gleason, PharmD, Prime Therapeutics, Eagan, MN; and Sachin Kamal-Bahl, PhD, Pfizer, New York, NY. The panel members shared their concerns regarding how various perspectives may be gathered, as well as how these newer value frameworks may influence decision makers.

The Summit closed with ISPOR Chief Science Officer Richard Willke, PhD returning to the podium to provide some final remarks. He noted that while topics presented during this Summit might not change practices today, they will help facilitate long-term improvements to value assessment frameworks. And it’s ideas like these that will spark experimentation, take root in future research efforts, be tried out and refined, and eventually become accepted approaches in our field. Doing this well is crucial to today’s patients and the patients of tomorrow. ●

Additional Information:

Presentation slides from this Summit are publicly available at <https://www.ispor.org/conferences-education/conferences/past-conferences/ispor-summit-2018/conference-presentations>. In addition, video recordings of all Summit sessions will be released as a webinar series beginning in early 2019; more information about these webinars will be released soon at www.ispor.org.

ISPOR would like to thank the Duke-Margolis Center for Health Policy and Biogen for their generous support of the 2018 ISPOR Summit.



The following highlighted articles appear in the November and December 2018 issues of *Value in Health* and the December 2018 issue of *Value in Health Regional Issues*.

For more information on *Value in Health*, visit: www.ispor.org/publications/journals/value-in-health.

For more information on *Value in Health Regional Issues*, visit: www.ispor.org/publications/journals/value-in-health-regional-issues.

Value in Health November 2018

METHODOLOGY

Calculating the Expected Value of Sample Information Using Efficient Nested Monte Carlo: A Tutorial

Anna Heath, Gianluca Baio

The authors investigated whether valuations of health states were affected by the differences in wording between EQ-5D-Y and EQ-5D-3L and by the perspective taken in the valuation exercise (child or adult).

SYSTEMATIC LITERATURE REVIEW

A Systematic Review of Patient-Reported Satisfaction With Oral Medication Therapy in Patients With Type 2 Diabetes

Yu Wang, Matthew Perri

The authors provide a comprehensive comparative evaluation of the psychometric properties of satisfaction with medication surveys used for patients with type 2 diabetes in clinical trials.

Value in Health December 2018

ECONOMIC EVALUATION

Cost-Effectiveness of a Comprehensive Approach for Hypertension Control in Low-Income settings in Argentina: Trial-Based Analysis of the Hypertension Control Program in Argentina

Federico Augustovski; Raul Chaparro; Alfredo Palacios; Lizheng Shi; Andrea Beratarrechea; Vilma Irazola; Adolfo Rubinstein; Jiang He; Andreas Pichon-Riviere; Katherine Mills

Among low-income patients with uncontrolled hypertension in Argentina, this study found that a multicomponent intervention led by community health workers was cost-effective.

METHODOLOGY

A Method to Predict Entry of Generic Drugs

Reed Beall; Jonathan Darrow; Aaron Kesselheim

In this article, the authors develop and test a method for approximating generic entry on top-selling drugs.

PATIENT-REPORTED OUTCOMES

A Rights-based Approach for Service Providers to Measure the Quality of Life of Children With a Disability

Elise Davis; Dana Young; Kim-Michelle Gilson; Elena Swift; Jeffrey Chan; Lisa Gibbs; Utsana Tonmukayakul; Dinah Reddihough; Katrina Williams

The authors identify the best instruments for service providers to measure the quality of life of children with a disability, with a focus on their alignment with the Convention on the Rights of Persons with a Disability.

Value in Health Regional Issues December 2018

ECONOMIC EVALUATION

Post-Introduction Study of Cost-Effectiveness of Pneumococcal Vaccine PCV10 From Public Sector Payer's Perspective in the State of Santa Catarina, Brazil

Emil Kupek; Ilse Viertel

The authors evaluate cost-effectiveness of pneumococcal vaccine PCV10 in the routine immunization program for <1 year old children in Brazil by a post-introduction study.

Análisis de costo de la enfermedad, del tratamiento, las complicaciones e intervenciones de la hipercolesterolemia en México en 2016

German Baeza Cruz

The authors describe the costs and economic impact of the care of patients diagnosed with hypercholesterolemia in Mexico in 2016.

Análisis de los determinantes socioeconómicos del gasto de bolsillo en medicamentos en seis zonas geográficas de Panamá

Victor Hugo Herrera Ballesteros

The authors characterize private out-of-pocket spending on medicines based on sociodemographic and socioeconomic determinants.

FROM THE JOURNALS

A Year of Growth and Expansion: *Value in Health* in Review

Michael F. Drummond, MCom, DPhil, University of York; UK
C. Daniel Mullins, PhD; University of Maryland-Baltimore; USA



During our tenure as Editors-in-Chief of *Value in Health*, never before have we experienced the level of growth and expansion of the journal than we have seen in the past 18 months. As many of you know, *Value in Health* increased the frequency of publication from 8 to 12 issues this year. Publishing 4 additional issues in 2018 has allowed us greater flexibility in scheduling high impact articles for publication.

Data released earlier this year from the *Journal Citation Reports* show that *Value in Health* earned an impact factor score of 5.494. The journal has consistently demonstrated double-digit percentage growth in its impact factor score for the past 5 years. *Value in Health* ranks 3rd among 94 journals in the Health Care Sciences and Services category; 3rd among 79 journals in the Health Policy and Services category; and 6th among 353 journals in the Economics category (see Table for rankings of the top 10 journals in each category).

The sidebar on the right illustrates how articles published in 2017 are currently being cited in the literature. This list of the top cited papers from 2017 includes 4 articles from the journal's Special Issue on Value Assessment Frameworks and 1 ISPOR Good Practices for Outcomes Research report on *Mapping to Estimate Health-State Utility from Non-Preference-Based Outcome Measures*. Several papers on the list (including one of the top-cited papers) explore different applications of the EQ-5D-5L instrument. Others examine diverse topics such as the use of surrogate endpoints in health policy (Ciani, et al), real-world data in health technology assessment (Makady, et al), and emerging guidelines for patient engagement in research (Kirwan, et al).

So far in 2018, the journal has published a series of papers from the ISPOR Special Task Force Report on US Value Assessment Frameworks [February], 2 ISPOR Good Practices for Outcomes Research Reports (ie, *Application of Constrained Optimization Methods in Health Services Research* >

Top Cited Articles Published in *Value in Health* in 2017

Estimating an EQ-5D-5L Value Set for China.

Luo N, Liu G, Li M, Guan H, Jin X, Rand-Hendriksen K.
Value Health. 2017;20(4):662-669. [19 citations]

Time to Review the Role of Surrogate End Points in Health Policy: State of the Art and the Way Forward.

Ciani O, Buyse M, Drummond M, Rasi G, Saad ED, Taylor RS.
Value Health. 2017;20(3):487-495. [19 citations]

Using Cost-Effectiveness Analysis to Address Health Equity Concerns.

Cookson R, Mirelman AJ, Griffin S, et al.
Value Health. 2017;20(2):206-212. [19 citations]

Policies for Use of Real-World Data in Health Technology Assessment: A Comparative Study of Six HTA Agencies.

Makady A, Ham RT, de Boer A, Hillege H, Klungel O, Goettsch W.
Value Health. 2017;20(4):520-532. [16 citations]

Emerging Guidelines for Patient Engagement in Research.

Kirwan JR, de Wit M, Frank L, et al.
Value Health. 2017;20(3):481-486. [16 citations]

Development of an Official Guideline for the Economic Evaluation of Drugs/Medical Devices in Japan.

Shiroiwa T, Fukuda T, Ikeda S, Takura T, Moriwaki K.
Value Health. 2017;20(3):372-378. [15 citations]

Mapping to Estimate Health-State Utility from Non-Preference-Based Outcome Measures: An ISPOR Good Practices for Outcomes Research Task Force Report.

Wailoo AJ, Hernandez-Alava M, Manca A, et al.
Value Health. 2017;20(1):18-27. [15 citations]

Quality Control Process for EQ-5D-5L Valuation Studies.

Ramos-Goñi JM, Oppe M, Slaap B, Busschbach JJV, Stolk E.
Value Health. 2017;20(3):466-473. [13 citations]

Instrument-Defined Estimates of the Minimally Important Difference for EQ-5D-5L Index Scores.

McClure NS, Sayah FA, Xie F, Luo N, Johnson JA.
Value Health. 2017;20(4):644-650. [11 citations]

Value Assessment Frameworks for HTA Agencies: The Organization of Evidence-Informed Deliberative Processes.

Baltussen R, Paul Maria Jansen M, Bijlmakers L, et al.
Value Health. 2017;20(2):256-260. [11 citations]

The Probabilistic Efficiency Frontier: A Framework for Cost-Effectiveness Analysis in Germany Put into Practice for Hepatitis C Treatment Options.

Mühlbacher AC, Sadler A.
Value Health. 2017;20(2):266-272. [11 citations]

Developing a Value Framework: The Need to Reflect the Opportunity Costs of Funding Decisions.

Sculpher M, Claxton K, Pearson SD.
Value Health. 2017;20(2):234-239. [11 citations]

FROM THE JOURNALS



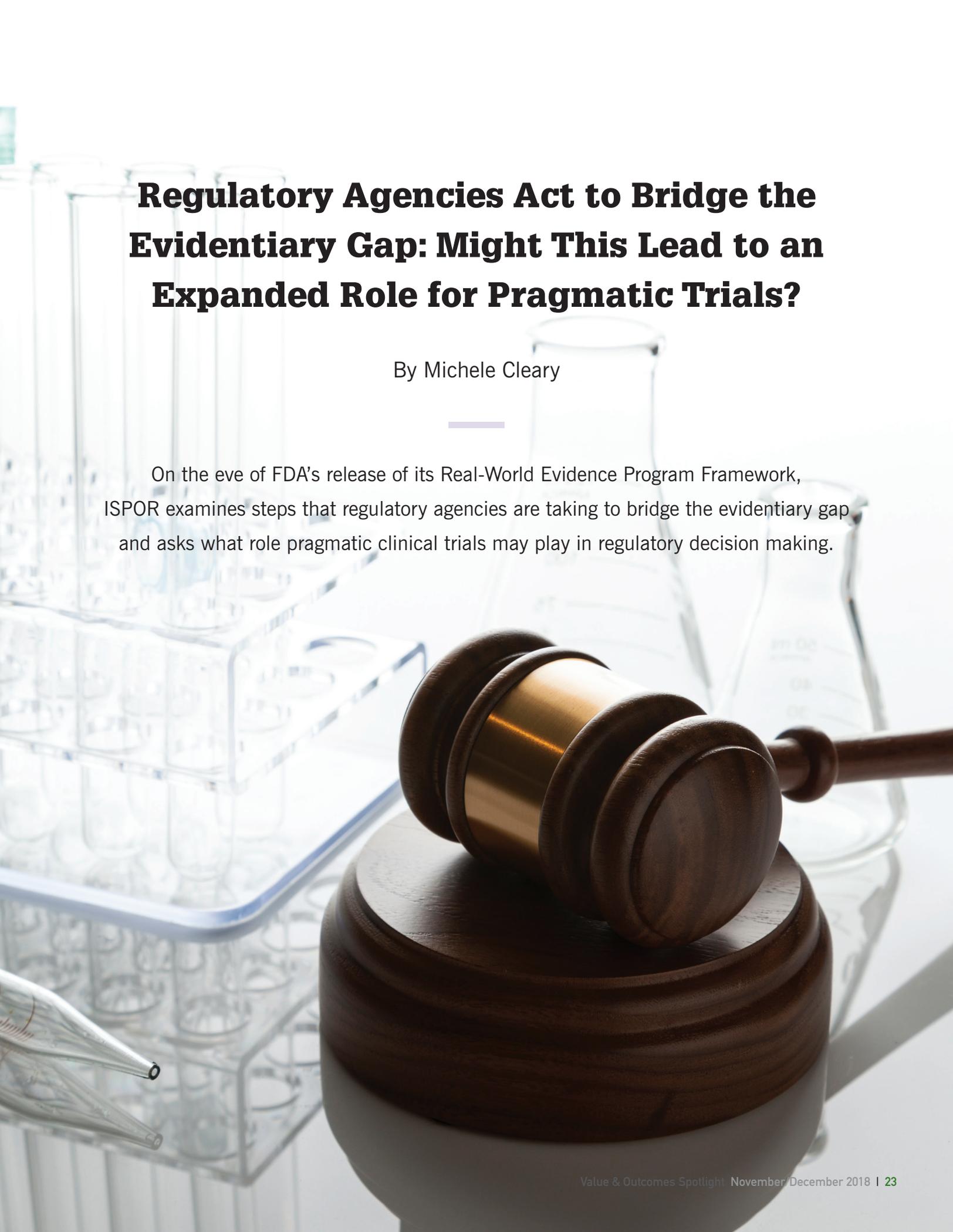
[September]; and *Economic Analysis of Vaccination Programs* [October]), each published with accompanying editorials. We have also published 4 themed sections (representing a combined total of 26 articles, editorials, and commentaries) on the following topics: Affordability in Healthcare (March); PhRMA Foundation Challenge Awards (April); Rare Diseases: Addressing the Challenges in Diagnosis, Drug Approval, and Patient Access (May); and Assessing the Value of Next-Generation Sequencing (September).

In addition, we are currently working on future themed sections on the EQ-5D, Curative Therapies, Health Technology Assessment Around the World, and a special collection of papers that celebrate the journal's 20th anniversary. So, keep reading...we have plenty of exciting content and special features coming your way in 2019. ●

Table. Top 10 High Impact Journal Rankings in 3 Content Categories

RANK	HEALTH CARE SCIENCES AND SERVICES	HEALTH POLICY AND SERVICES	ECONOMICS
1	BMJ Quality & Safety	BMJ Quality & Safety	Quarterly Journal of Economics
2	Millbank Quarterly	Millbank Quarterly	Journal of Human Resources
3	Value in Health	Value in Health	Journal of Economic Growth
4	Health Affairs	Health Affairs	Economic Geography
5	Academic Medicine	Implementation Science	Journal of Economic Perspectives
6	Journal of Medical Internet Research	Pharmacoeconomics	Value in Health
7	JMIR mHealth and uHealth	Medical Care	Journal of Finance
8	Health Technology Assessment	Journal of Health Economics	Journal of Political Economy
9	Medical Education	Administration and Policy in Mental Health and Mental Health Services Research	Journal of Financial Economics
10	Implementation Science	Journal of Patient Safety	American Economics Journal: Applied Economics

Data from 2017 Journal Citation Reports® (Clarivate Analytics, 2018).



Regulatory Agencies Act to Bridge the Evidentiary Gap: Might This Lead to an Expanded Role for Pragmatic Trials?

By Michele Cleary

On the eve of FDA's release of its Real-World Evidence Program Framework, ISPOR examines steps that regulatory agencies are taking to bridge the evidentiary gap and asks what role pragmatic clinical trials may play in regulatory decision making.

US and EU regulatory bodies have taken steps recently to broaden their use of real-world evidence (RWE) in regulatory decision making. As defined by the US Food and Drug Administration (FDA),^[1] RWE is the “clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data (RWD).” Both the FDA and the European Medicines Agency (EMA) have employed RWE in postapproval safety and efficacy studies. Now, pushed by the explosive rate of biomedical innovation, these agencies are exploring ways to utilize new RWD sources to supplement randomized clinical trial (RCT) data — expanding the “evidence mix,” accelerating the approval process, and delivering much-needed therapies to patients in need.

As regulatory agencies expand their interest in RWE beyond postapproval safety and efficacy analyses, the pharmaceutical industry faces uncertainty. Pharmaceutical companies have long used RWE to inform marketing decisions, economic modeling, and pricing — even expanding its use in earlier stages of the clinical drug development pipeline for “go/no-go” decision making. But now with regulatory bodies expanding their acceptance of RWE, companies must ask whether their RWE plans are sufficient to meet both regulatory and payer demands.

WHEN THE GOLD STANDARD IS NO LONGER SUFFICIENT

With their high degree of internal validity, RCTs are a good fit to demonstrate causality. However, their inherent design — treatment randomization, inclusion/exclusion criteria, standardized follow-up procedures — also limits their external validity, thereby limiting the ability to extrapolate drug efficacy conclusions to drug effectiveness in the practice setting. This difference between clinical research and practice — frequently referred to as the evidentiary gap — is driving regulatory bodies to explore broader use of RWD and RWE.

THE APPEAL OF RWD

RWD can improve our understanding of how safe and effective a drug is in actual clinical practice, uncovering valuable insights regarding both effectiveness and safety that may not be seen within the constraints of clinical trials. Common RWD sources include disease registries, administrative claims data, electronic health records, and a wide range of new biosensor data. The FDA has had significant experience with claims data via Sentinel for safety and effectiveness inquiries. For instance, the FDA recently incorporated effectiveness information derived from a prospective claims data analysis into vaccine labeling. Administrative claims data can help us better understand the natural history of disease, treatment patterns, treatment-specific health services utilization patterns, and health outcomes relative to comparator products. Plus, RWD can generate more cost- and time-efficient evidence than RCT data alone. As the quality and variety of RWD improve, interest in utilizing RWD continues to grow.

While RWD can potentially supplement RCT evidence, RWD present their own methodological challenges stemming from non-random treatment allocation and data quality (incomplete or missing data fields), for example. In addition, study management issues may complicate implementation. For instance, informed consent privacy and data integration also need to be addressed and protocols developed to maintain data integrity. Missing data, accuracy of data; personnel capturing the data may not all be following the same protocols. While statistical methods

(eg, propensity scoring, instrumental variables) address many of these concerns, uncertainty surrounding how RWD should be incorporated into RCT data for effectiveness assessments abound, especially as it pertains to regulatory decision making.

WHERE MIGHT RWE FIT IN REGULATORY DECISION MAKING?

RWE has the potential to inform regulators on many fronts, providing critical insight into disease epidemiology, burden of illness, and current treatment standards. It can help refine clinical practice guidelines and illuminate relative value. And such information can help manufacturers prioritize and streamline drug development, accelerating evidence generation to support label expansion for specific products. Coupled with newer RWD sources and next-generation analytics, RWE presents an enormous opportunity to improve and accelerate regulatory decision making. But concerns persist, especially surrounding data accuracy, reproducibility, and incomplete data. Claims data are created to support reimbursement, not research, and hence could introduce unwanted bias into research. EHR data present similar risks. Therefore, in order to maximize the value of RWE into supporting decision-making requires the most appropriate data sources and analytics.

Now regulatory bodies are exploring how best to use RWE to support and/or supplement pre-market decisions, asking when or whether RWE should be used to evaluate new therapies or new indications for existing products. There had been a lack of guidance on systematic approaches for the inclusion, analysis, and interpretation of RWD for regulatory decision making. These new regulatory initiatives explore appropriate study designs for generating RWD and developing further analytic methods for synthesis of RWD from different sources through initiatives.

A NEW FUTURE FOR RWE UNDER THE 21ST CENTURY CURES ACT

Signed into law in late 2016, the 21st Century Cures Act aimed to modernize research, accelerate treatment discoveries, and expedite access to new medicines.^[2] The Act included initiatives

But now with regulatory bodies expanding their acceptance of RWE, companies must ask whether their RWE plans are sufficient to meet both regulatory and payer demands.

to incorporate patient perspectives into drug development (Section 3002) and rules clarifying how pharmaceutical companies may share healthcare economic information with payers and formulary decision makers (Section 3037).

The Cures Act also mandated the FDA to establish a protocol for integrating RWE into regulatory decision making (Section 3022) — expanding its current use in postmarketing surveillance capacities to perhaps becoming integral to all phases of medical product development. The law directs the FDA to develop guidelines that define appropriate uses of RWD, that evaluate how RWE may be used to support approval of new indications for approved drugs, and to support or satisfy postapproval study requirements.

By the end of 2018, the FDA is required to draft a framework for the implementation of the RWE program that describes sources of RWE (eg, ongoing safety surveillance, observational studies, registries, claims, and patient-centered outcomes research activities); the gaps in data collection activities; the standards and methodologies for collection and analysis; and the priority areas, remaining challenges, and potential pilot opportunities. Draft guidance on circumstances where RWE can be used and standards for use is slated for October 2021.

EMA EXPLORES RWE INITIATIVES

Like the FDA, the EMA has a long history of using RWE in postauthorization drug safety surveillance studies.[3-5] Recently, the EMA has introduced 2 initiatives that utilize RWE to accelerate the authorization of new treatments.

- The Adaptive Pathways (AP) approval path helps accelerate access to products serving areas of unmet need — rare conditions where sufficient RCT data may be difficult to generate.[6,7] The AP approval path permits limited approval for these targeted populations through iterative evidence generation — pragmatic and real-world studies designed to complement RCTs.
- The EMA's Clinical Trial Regulation (536/2014) expands the definition of “clinical trial” to 3 categories: clinical trials, noninterventional studies, and low-interventional clinical trials.[8] The low-interventional clinical trial begins with a noninterventional study of an authorized drug and incorporates some form of additional diagnostic or monitoring procedures (procedures that expose patients to minimal risk or impact). These low-intervention clinical trials are used to investigate safety and efficacy questions that have arisen since authorization — often through a pragmatic clinical trial design.[9]

ASIAN REGULATORY AGENCIES EXPLORING RWE

In Asia, many countries are exploring the use of RWE in regulatory decisions, with great variability by country stemming largely to differences in RWD sources. Japan appears to be most proactive in the region with its Medical Information Database Network, a repository of clinical data that is expected to be used in regulatory decision making. Singapore's drug regulatory agency, the Health Sciences Authority (HSA), is exploring an Adaptive Licensing pathway similar to the one recently piloted by the EMA. In the Philippines, companies are required to conduct postmarketing studies on all marketed drugs to assess safety, tolerability, and effectiveness across more diverse populations. Finally, both China and India have demonstrated growing interest in the implications and applications for RWE in product development.[10]

CAN PRAGMATIC CLINICAL TRIALS HELP FILL THE EVIDENTIARY GAP?

As regulatory agencies explore new uses and standards for RWE, the acceptance of pragmatic clinical trials (PCTs) remains unclear. PCTs present a unique balance between RCTs and observational trials common with other types of RWD. Embedded within a more realistic clinical practice environment, PCTs offer a broader patient mix and outcome measures, as well as more streamlined data collection (possibly with linkages to EHRs), than what are often captured with most RCTs. Hybrid trials — combining elements from both clinical and pragmatic clinical trials — could provide further insight into real-world treatment effectiveness.

Yet challenges persist. PCTs are often plagued with incomplete or inaccurate data — both issues that may greatly limit their use in regulatory settings. Many pragmatic trials rely on RWD sources, such as registries or EHRs, that allow easier subject recruitment and study implementation, thus keeping research costs low and time-to-completion short. Clear identification of product effects is critical to regulatory decision making. PCTs may be too simplified for regulatory needs.

AWAITING REGULATORY GUIDANCE

The FDA will be sharing its framework for RWE (Section 3022) any day. Meanwhile, the EMA has just begun to evaluate the use of RWE under 536/2014. And finally, regulatory agencies across Asia are debating their RWE strategies.

Real-world data can improve our understanding of how safe and effective a drug is in actual clinical practice, uncovering valuable insights regarding both effectiveness and safety that may not be seen within the constraints of clinical trials.

Uncertainties abound. How do these bodies differ in their acceptance/view of RWD? Will all bodies take a similar view of retrospective data? Will there be a place for PCTs in these new RWE regulatory initiatives? Or will regulatory bodies look strictly to observational studies, free from research intervention, treatment assignment, inclusion/exclusion criteria, or monitoring protocols? And finally, how should pharmaceutical companies prepare for these changes? How should they refine their RWE research agendas to meet the needs of all regulatory bodies?

To help clarify their response, the FDA is currently funding a study to determine whether observational methods can be used to replicate drug-effectiveness findings from roughly 30 RCTs. The FDA believes this research will better inform their understanding of observational study methods and whether these methods should be applied to drug effectiveness evaluations.[11] The Agency notes: “Further research is needed to determine when large data sets and statistical methods are sufficient to correct for systematic bias in sampling, ascertainment, or missing data that may arise in observational studies—a particular problem with retrospective studies in which less well-characterized patients limit adjustments for confounders.”

The FDA has reinforced its view regarding the importance of patient perspectives when discussing RWE:

“...if research is to fulfill its goal of being patient centric, it will be necessary to leverage technological advances, such as mobile health, to capture the patient experience beyond the clinical delivery system and establish a more comprehensive picture of how medical products function beyond the controlled confines of traditional randomized clinical trials.”

In recent communication with ISPOR, the FDA has stated an interest in “exploring pragmatic approaches to each stage of a >

clinical trial.”[12] However, they stated that while they were open to a variety of potential sources for RWD, they articulated 3 key considerations as they implement their RWE Program:

1. Whether the RWD are fit for use;
2. Whether the trial or study design used to generate RWE can provide the necessary scientific evidence to answer or help answer the regulatory question; and
3. Whether the study conduct meets FDA regulatory requirements.

The ISPOR/ISPE Task Force released their good practice guidelines for RWD studies of treatment and comparative effectiveness.[13] These recommendations coupled with the new regulatory guidance will be critical in supporting manufacturers meet regulatory expectations for RWE use in healthcare decision-making.

While there appears to be growing consensus across regulatory agencies regarding the benefit of increased real-world observations across all phases of drug development, questions remain. Clearly, RWE represent a cost-effective way to include unique groups (eg, rare diseases) into trials with iterative evidence generation. PCTs allow for longer follow-up periods and can incorporate patient-reported outcomes – attributes often missing from traditional RCTs. RWE can help manage trial expenses, thereby allowing for more affordable treatments to market faster.

RWE can help manage trial expenses, thereby allowing for more affordable treatments to market faster.

Much rides on the current FDA study of effectiveness studies mentioned above. Will results drive the FDA, EMA, and other regulatory bodies to accept RWE, and specifically PCTs, to expand real-world evidence of treatment effectiveness in real-world practice environments with novel patient populations? Or will the bias inherent in PCTs limit their use?

For now, waiting continues.

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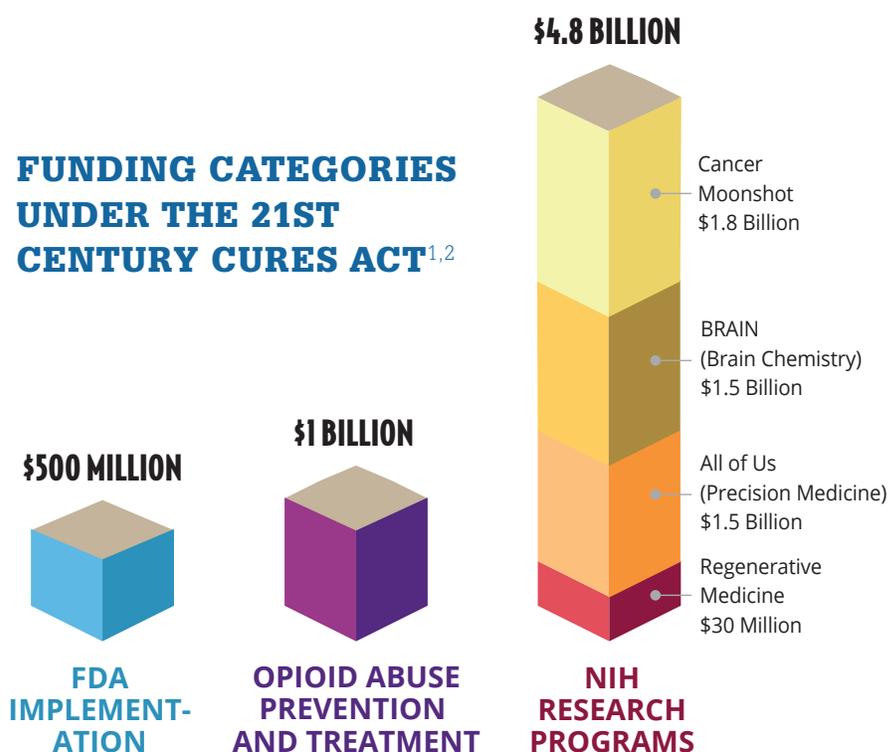
By the Numbers: Policy Changes from the 21st Century Cures Act

Section Editor: The ISPOR Student Network

TIMELINE FOR THE 21ST CENTURY CURES ACT³

- 2013** House Energy and Commerce Committee hearings started
- 1/6/2015** Introduced in the House
- 1/7/2015** Passed the House
- 10/6/2015** Passed the Senate with an amendment
- 11/30/2016** The House agreed to Senate amendment with further amendment
- 12/7/2016** The Senate agreed to House amendment
- 12/13/2016** Signed into law by President Barack Obama

FUNDING CATEGORIES UNDER THE 21ST CENTURY CURES ACT^{1,2}



FDA GUIDANCE MILESTONES⁵

DRAFT GUIDANCE ISSUED

- **12 Jun 2018:** Patient-Focused Drug Development: Collecting Comprehensive and Representative Input - Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders
- **13 Jun 2018:** Limited Population Pathway for Antibacterial and Antifungal Drugs - Guidance for Industry
- **13 Jun 2018:** Humanitarian Device Exemption (HDE) Program - Draft Guidance for Industry and Food and Drug Administration Staff

GUIDANCE TO BE RELEASED

- **13 Dec 2019:** Protection of human research subjects
- **13 Dec 2019:** Qualification of drug development tools
- **Date to be announced:** Novel clinical trial designs
- **Date to be announced:** Real world evidence

SOME NUMBERS ON THE 21ST CENTURY CARES ACT⁴

- VOTES IN THE HOUSE:** 392 IN FAVOR – 26 AGAINST
- VOTES IN THE SENATE:** 94 IN FAVOR – 5 AGAINST (1 NOT VOTING)
- SECOND-MOST LOBBIED HEALTHCARE BILL IN THE HISTORY**
- MORE THAN 1,400 REGISTERED LOBBYISTS WORKED ON THIS BILL**
- REGISTERED LOBBYISTS REPRESENTED MORE THAN 400 DIFFERENT ORGANIZATIONS**
- APPROXIMATELY HALF A BILLION DOLLARS WAS SPENT ON LOBBYING**

Contributors: Christy Choi, University of Minnesota; Jayesh Patel; Nazneen Shaikh; Shannon Vaffis, University of Arizona; Aakash Gandhi, University of Maryland; Koen Degeling, University of Twente

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³ National Institutes of Health, Implementation of Funding Plan for the NIH Innovation Projects Under the 21st Century Cures Act, Available from: <https://www.nih.gov/research-training/medical-research-initiatives/cures>

⁴ Sydney Lupkin, A Frenzy Of Lobbying On 21st Century Cures, *Kaiser Health News*; 2016. Available from: <https://khn.org/news/a-frenzy-of-lobbying-on-21st-century-cures/>

⁵ FDA.gov, US Food and Drug Administration - 21st Century Cures Act Deliverables, Available from: <https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCA/21stCenturyCuresAct/ucm562475.htm>

Recent Initiatives in US Drug Policy to Promote Innovation, Value, Access, and Affordability

Ambarish Ambegaonkar, PhD, APPERTURE LLC, Marlboro, NJ, USA, and Nneka Onwudiwe, PharmD, PhD, MBA, US Food and Drug Administration, Silver Spring, MD, USA

KEY POINTS

21st Centuries Cures Act aims to fuel rapid innovation in drug development and patient access to innovative medical technologies while enhancing the ability to communicate value of innovation.

American Patients First Blueprint aims to modulate the rapid growth in healthcare costs of innovation by increasing competition, negotiation, and affordability.

Stakeholder implications of the 2 policies are significant across the US healthcare marketplace and in particular for HEOR professionals who can have major impact on the execution of both policies initiatives.

Place of innovation in healthcare has reached a tipping point, and we are at the cusp of an era of curative therapies as well as those extending and enhancing quality of life. The promise of targeted immunotherapies in cancer, personalized gene therapy in rare disease, growth of biologic therapies, along with enhanced access to big data and digital innovation have fueled the US Market's tremendous appetite for healthcare innovation. However, innovation does not come without cost, which is a cause of daily discussion in national headlines. While overall pharmaceutical care costs have recently stabilized to a 1.4% annual increase, specialty products have continued to grow at an annual rate of 9%. [1] These cost and pricing trends have not been dented by the advent of competition, biosimilars, or any effective management strategy.

Value demonstration is now a cornerstone of any innovative healthcare intervention and is rapidly evolving with the availability of real-world evidence (RWE). Communication of this value to stakeholders, to enhance their decision making, is critical to the adoption and the contextualization of innovation, its cost, and its impact. Newer policy models that speed development and enhance regulatory pathways are required to further this innovation to ensure reach of its societal benefit. At the same time, managing costs and affordability takes critical priority. Two major policy initiatives in the last couple of years have been developed to address this fine balance, the 21st Century Cures Act and the American Patients First Blueprint. This article presents these key policy initiatives and their implications for stakeholders.

21ST CENTURIES CURES ACT

The 21st Century Cures Act (Cures Act) [2] passed the House of Representatives on November 30, 2016, and the Senate on December 7, 2016, and was signed into law on December 13, 2016, by President Obama. The Cures Act represents bipartisan legislation that provides \$6.3 billion for medical research over the next

several years to harness science, medicine, and technology to tackle challenges in healthcare. The Cures Act, formally known as HR 34, provides the FDA with the necessary resources to create a path for scientific advancements and patient access to innovative medical technologies. The key provisions in Title III of the Cures Act and other provisions that focus on medical product development build on the FDA's current efforts to streamline and transform regulatory activities. Subtitles A-D of Title III pertaining to medical product development and for patient access requires FDA compliance with statutory requirements and activities within the following subtitles and sections detailed below. Table 1 summarizes FDA's deliverables under Subtitles A-D of Title III of the Cures Act, as well as implementation and impact of the different subsections in the market. For example, the use of patient-reported outcome (PRO) data in drug development (eg, clinical endpoints) and commercial strategy can improve market differentiation and value. Likewise, competition-enhancing regulatory reforms as well as policies that promote innovation, market entry, and access can influence pharmaceutical prices.

SUBTITLE A: PATIENT FOCUSED DRUG DEVELOPMENT

More broadly, the provisions in Subtitle A, sections 3001-3004, under Title III of the Cures Act direct the FDA to incorporate patients' experiences, perspectives, needs,

Newer policy models that speed development and enhance regulatory pathways are required to further this innovation to ensure reach of its societal benefit.

and priorities in drug development and evaluation. For example, section 3001 directs the Secretary "following approval of an application submitted under section 505(b) of the Act or section 351(a) of the Public Health Service, at least 180

days after the date of enactment”, to make public a brief statement “regarding the patient experience data and related information, if any, submitted and reviewed as part of such application.” The data and information refer to patient experiences, patient-focused drug development tools, and other relevant information. In addition, the Cures Act considers patient experience data to encompass information: (1) collected by patients, family members, caregivers, patient advocacy groups, disease research foundations, researchers, or drug manufacturers; and (2) provide information about patients’ experiences with a disease or condition, “including— (a) the impact of such disease or condition, or a related therapy, on patients’ lives; and (b) patient preferences with respect to treatment of such disease or condition.” The patient-focused development provisions in Subtitle A create an opportunity for patient insights in drug development and benefit-risk assessment.

SUBTITLE B: ADVANCING NEW DRUG THERAPIES

The provisions in Subtitle B, sections 3011-3016, under Title III of the Cures Act aims to accelerate medical product development and approval processes and bring medical advances to the market faster and more efficiently. The Cures Act directs the Secretary, acting through the FDA, to establish a process for the qualification of Drug Development Tools for a proposed context of use, which includes determining the acceptability of a qualification submission based on scientific merit. Drug Development Tools (DDTs) (ie, biomarkers, clinical outcome assessments (COAs), and animal models) are methods, materials, or measures that have the potential to facilitate drug development and market entry. The rare disease space is another example where the Cures Act aims to bring new drug therapies to the market to address an unmet need. Section 3012 is intended to “(1) facilitate the development, review, and

approval of genetically targeted drugs and variant protein-targeted drugs to address an unmet medical need in one or more patient subgroups, including subgroups of patients with different mutations of a gene, with respect to rare diseases or conditions that are serious or life-threatening; and (2) maximize the use of scientific tools or methods, including surrogate endpoints and other biomarkers” in clinical research (eg, clinical endpoints to assess efficacy, enrichment designs). Similarly, the provision in section 3013 on the reauthorization program for rare pediatric diseases will allow individuals from birth to 18 years to gain access to potentially life-saving and life-changing treatments by accelerating and promoting development of therapies in this space.

SUBTITLE C: MODERN TRIAL DESIGN AND EVIDENCE DEVELOPMENT

Included in the Cures Act are provisions in Subtitle C on modern approaches to designing and conducting clinical trials. Section 3021, novel clinical trial designs under Subtitle C directs the FDA to incorporate complex adaptive and other novel trial designs into proposed clinical protocols and applications for new drugs and biological products. The Secretary, acting through the FDA, shall update or issue guidance addressing the use of novel approaches such as complex adaptive and other novel trial designs in clinical development. This provision helps us to address the needs of innovation and efficiency in clinical trial conduct while maximizing patient access. Section 3022 on RWE directs the FDA to evaluate how such data can be used to support approval of new indications for approved drugs or to support or satisfy post-approval study requirements. The law also requires a draft framework for implementation for the RWE program that includes information describing the sources of RWE, “including ongoing safety surveillance, observational studies, registries, claims, and patient-centered outcomes research activities; the gaps in data collection activities; the standards and methodologies for collection and analysis; and the priority areas, remaining challenges, and potential pilot opportunities.” In discussing the acceptance of RWE to support regulatory decisions, the FDA has used historical controls in rare disease drug development and approval (eg, Myozyme, Carbaglu). >

Table 1: Key sections of 21st Century Cures Act, Statutory Deliverables, and Potential Impact in the Market Place³

Title III Section Number	Title III Subsection	Statutory Deliverable	Impacts
3001	Patient experience data		Value
3002	Patient-focused drug development guidance	Plan, Draft & Final Guidance	Value
3004	Report on patient experience drug development	Public Report	
3011	Qualification of drug development tools	Plan, Public Report, Draft & Final Guidance, FR Notice, Public Meeting, Public Report	Innovation, Access
3014	GAO study of priority review voucher programs	GAO Report	Access
3016	Grants for studying continuous manufacturing	Grants	Access, Pricing
3021	Novel clinical trial designs	Public Meeting, Draft Guidance, Final Guidance	Innovation
3022	Real world evidence	Plan, Framework, Draft Guidance, Final Guidance	Access, Pricing, Innovation
3023	Protection of human research subjects	Regulation or Guidance, Report to Congress	Access
3024	Informed consent waiver or alteration for clinical investigations	Other	Innovation
3031	Summary level review	Other	
3034	Guidance regarding devices used in the recovery, isolation, or delivery of regenerative advance therapies	Final Guidance	Pricing
3035	Report on regenerative advanced therapies	Report to Congress	Pricing, Value
3036	Standards for regenerative medicine and regenerative advanced therapies	Plan	Innovation
3038	Combination product innovation	Final Guidance	Value

Source Adapted from: 21st Century Cures Act Deliverables. <https://www.fda.gov/regulatoryinformation/lawsenforcedbyfda/significantamendmentstothehdact/21stcenturycuresact/ucm562475.htm>

SUBTITLE D: PATIENT ACCESS TO THERAPIES AND INFORMATION

The provisions in Subtitle D, sections 3032-3033, increase patient access to new drug therapies through the expanded access policy and accelerated approval for regenerative advanced therapies (eg, Regenerative Medicine Advanced Therapy (RMAT) designation program) and provide more timely access to potentially life-saving therapeutic alternatives. The provisions in section 3031 to 3033 could present an opportunity to address pricing and access for therapies showing evidence of clinical effect in early stages of development, for example.

Section 3037 on healthcare economic information (HCEI), which amended FDAMA 114, expands the scope of drug manufacturers' communication to payers, formulary committees, or other similar entities about the value of their products. The Cures Act defines HCEI as any analysis (including the clinical data, inputs, clinical or other assumptions, methods, results, and other components underlying or comprising the analysis) that identifies, measures, or describes the economic consequences, which may be based on the separate or aggregated clinical consequences of the represented health outcomes of the use of a drug [2]. The preapproval information exchange (eg, product pricing information) under this provision provides an opportunity for better communication on product value.

AMERICAN PATIENTS FIRST BLUEPRINT

In May 2018, the White House released the American Patients First (APF) Blueprint [4] aimed to lower drug prices and reduce out-of-pocket costs. The APF blueprint outlines President Trump's agenda to spur new entrants, improve competition, and create incentives for pharmaceutical companies to lower list prices, amongst other things. The administration's vision to lower drug prices and reduce out-of-pocket costs is centered around key issues identified as challenges in the pharmaceutical market, namely rebates and discounts that favor high list prices, patent exclusivity, the expansion of the 340B drug discount program, international price controls, and government programs lacking modern negotiation tools. The Health and Human Services Secretary (HHS) introductory message in the APF blueprint echoed the administration's commitment to bring immediate relief while also delivering long-term reforms. The

secretary states that "the time to act is now: not only are costs spiraling out of control, but the scientific landscape is changing as well." HHS has identified 4 challenges in the American pharmaceutical market:

1. High list prices for drugs
2. Seniors and government programs overpaying for drugs due to lack of the latest negotiation tools
3. High and rising out-of-pocket costs for consumers
4. Foreign governments free-riding from American investment in innovation

In the APF Blueprint, HHS proposes to address these challenges using 4 key strategies for reform: (1) improved competition; (2) better negotiation; (3) incentives for lower list prices; and (4) lowering out-of-pocket costs. This is to be accomplished through 2 phases: 1) actions the President may direct HHS to take immediately and 2) actions HHS is actively considering, on which feedback is being solicited. The blueprint introduced immediate actions and proposals to lower list prices and out-of-pocket costs[4]:

Incentives for Lower List Prices

Immediate Actions

- FDA evaluation of requiring manufacturers to include list prices in advertising
- Updating Medicare's drug-pricing dashboard to make price increases and generic competition more transparent

Lowering Out-of-Pocket Costs

Immediate Actions

- Prohibiting Part D contracts from preventing pharmacists telling patients when they could pay less out-of-pocket by not using insurance
- Improving the usefulness of the Part D Explanation of Benefits statement by including information about drug price increases and lower cost alternatives

These recent policy initiatives will likely have short and long-term implications to key stakeholders.

Implications of these policy initiatives: are significant across the 5 key stakeholders:

1. **Regulatory Authorities:** Should have a clear mandate in speeding the process of drug development for rare diseases (eg, validation of biomarkers); driving use of RWE of patient origin in drug development; enhancing sharing of information; and clarifying FDA authority on development of orphan drugs. Furthermore, the APF Blueprint provides new rules for the FDA to govern the implementation of pricing

transparency and disclosure in direct-to-consumer advertising.

2. **Payer Organizations:** Regulations on sharing HCEI will allow rapid determination of value assessment, formulary decision making, and medical policy implementation. The potential to accelerate the value-based purchasing per the APF Blueprint will allow plans to negotiate innovative agreements with manufacturers.
3. **Value Assessment Organizations:** Will need to recognize the potential of patient-derived RWE in their assessments beyond cost-effectiveness and budget impact analysis.
4. **Patients:** Enhanced access to compassionate-use medications, expedited regulatory pathways for rare diseases, and enhanced visibility to drug pricing will provide significant choice in making decisions impacting their care.
5. **Pharmaceutical Manufacturers:** Speeding trial performance, mitigating paperwork and regulations on review, enhanced trial designs, and guidance on combination products will drive innovation to market. Balancing the ability to get innovation to market will be the responsibility to demonstrate value through pricing strategy reform and lowering overall healthcare system costs. HEOR professionals will significantly benefit from the provisions of the new policy initiatives, as they are the key experts at the heart of developing RWE, communicating HCEI to payers, and developing value-based contracts.

Successful implementation of the Cures Act and policies outlined in the APF Blueprint has the potential to remove obstacles and unnecessary cost to the healthcare system. The key to their actual impact will depend on the implementation plan, timing, and absorption of the policy initiatives into the healthcare marketplace.

Note: This article reflects the views of the author and should not be construed to represent the FDA's views or policies.

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Let There Be Light: Improving Transparency in the Biopharmaceutical Supply Chain

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KEY POINTS

The biopharmaceutical supply chain is opaque; who pays what, to whom, or why remains unknown. Moreover, most participants vigorously defend this opacity as essential to securing the most favorable prices for patients.

Improving the transparency of the various transactions between the participants in the biopharmaceutical supply chain is a necessary step in making medicines affordable, but probably is not sufficient on its own.

Transparency has demonstrated benefits in many other areas—with people expecting disclosure of information—from mortgages to specific aspects of financial trading and nutrition labeling to fuel economy and workplace safety.

The renowned Dutch artist M.C. Escher said, “We adore chaos because we love to produce order.” This sentiment seems appropriate to the contentious challenge of making prescription medicines more affordable and available. Trying to understand the US biopharmaceutical supply chain—arguably one of the world’s most complex markets—mirrors Escher’s 1953 lithograph *Relativity*, full of impossibly interlocking stairways and multiple forces of gravity understandable only through viewpoint variation.

Developing novel medicines that prevent, manage, or cure conditions—and ultimately improve human welfare—represents an extraordinary human achievement. These medicines affect public health, social equity,

price increases, except through the power of competition and the bargaining power of large buyers such as retail pharmacy chains and prescription drug insurance plans, usually acting through pharmacy benefit managers (PBMs). Most other industrialized nations have centralized buying power for drugs. Governments of these nations generally can exclude drugs from formularies, and many also use essential medicines lists to guide purchasing decisions. In the United States, PBMs have consolidated bargaining power in the biopharmaceutical supply chain to some extent, but it is not clear how much savings are shared (if at all) with patients. Some manufacturers have begun to discuss eliminating their current discounts to PBMs and simply offering lower prices.

Akin to Escher’s *Relativity*, it’s clear that the magnitude and effects of the problem—and how each participant conceives and presents it—is relative to their interests and varies with their position

and economic development. But their development comes neither cheaply nor easily. Many drug candidates fail for each success. Those that do succeed require millions to billions of dollars in research and development costs. Some drugs carry very high prices that few people in the United States can afford. The public has long desired concrete steps to increase availability and affordability of prescription drugs, but to this point policies have not yet culminated in effective solutions.

Currently, potential profits create incentives for investment in biopharmaceutical research and development. Without this—in the current patents-based system—investment for new drug development could shrink. While patent protection enhances the availability of new drugs, eventual competition from generic products hopefully will enhance affordability. Health insurance mitigates the effects of high prices on patients but raises other concerns.

The United States today has no meaningful control of either launch prices or annual

Concurrently, bargaining power of the federal government as a purchaser is limited by legislation. By no coincidence, the United States pays higher prices for branded drugs than virtually all industrialized nations and devotes a greater fraction of its total spending on supply chain intermediaries than do other countries.

Recently, prescription drug pricing has gained increased prominence. In 2018, the White House released *American Patients First*, a blueprint to lower drug prices. A report from the Council of Economic Advisers outlined policy reforms: *Reforming Biopharmaceutical Pricing at Home and Abroad*. For-profit and non-profit institutions continue to disseminate position statements—often stating the same problem from different vantage points with their preferred solutions. Akin to Escher’s *Relativity*, it’s clear that the magnitude and effects of the problem—and how each participant conceives and presents it—is relative to their interests and varies with their position. One can also readily find examples of how each segment of the >

biopharmaceutical supply chain blames other participants for high and rising prices.

Early in 2018, the National Academies of Sciences, Engineering, and Medicine also published *Making Medicines Affordable: A National Imperative*. This report recommends various pathways—through congressional legislation and federal and state agency actions as well as industry-based approaches—to improve the affordability of prescription drugs without discouraging the future development of new and more effective drugs. One key recommendation, with 3 actions, focused on improved understanding of how the biopharmaceutical supply chain works, who the participants are, and what their financial transactions and profit margins are.

In brief, the first action centers on gathering quarterly information, at the National Drug Code Level, from insurance plans (about average net prices paid for drugs, including patient cost-sharing) and from biopharmaceutical companies (about average net volume of and prices for drugs across each sales channel, including discounts to PBMs and insurance plans). These data would illuminate which entities capture what share of payment along the supply chain. The second action focuses on requiring biopharmaceutical companies to submit an annual public report stating list prices, (changes to) rebates and discounts to payers, and the average net price of each drug sold in the United States to identify all the net drug price increases exceeding the growth of consumer price index. The final action expands disclosure requirements on all sources of income by organizations in the biopharmaceutical sector that are exempt from income taxes under the Internal Revenue Code. Some of these organizations appear to rely heavily on biopharmaceutical industry support.

Improving the transparency of the various transactions between the participants in the biopharmaceutical supply chain is a necessary step in making medicines affordable. In this regard, we can fruitfully examine how transparency works within the finance industry. Regulators devote considerable effort to making financial markets transparent, usually by imposing disclosure and reporting requirements and

by creating incentives for transactions to occur through public exchanges. The belief behind this approach is that transparency will benefit customers by enabling them to make informed decisions. Thus, the financial industry has rules governing “market-sensitive” data and “insider trading,” designed to ensure that all market participants have equal access to potentially influential information.

The United States today has no meaningful control of either launch prices or annual price increases, except through the power of competition and the bargaining power of large buyers such as retail pharmacy chains and prescription drug insurance plans, usually acting through pharmacy benefit managers.

Information alone provides many benefits in financial markets. With sufficient information, the market effectively “polices” suppliers. Financial markets operate with a broad sense that competition squeezes out bad behavior, thus reducing the need for regulation. In some cases, regulation extends further to protect consumers. Reserve requirements of insurance companies provide one example: life insurance companies must maintain financial reserves at least equal to their outstanding obligations. But in general, financial markets rely relatively strongly on competition rather than regulation to limit undesirable behavior.

Transparency has also demonstrated benefits in several other areas. From nutrition labeling (as well as on content and benefit claims) to occupational safety policies in the workplace, people expect transparent disclosure of information. Mandatory posting of fuel economy data on all new vehicles helps consumers make prudent choices about vehicle purchases. The federal Truth in Lending Act mandates information regarding mortgages for prospective home owners in the real estate market, thus improving their ability to make prudent decisions both about

the choice of mortgage and the financial obligations that they can afford. Many similar examples regarding the benefits of information exist.

In contrast, the prescription drugs market, especially the highly complex supporting supply chain, is opaque. Little to no relevant data illuminate who pays what and to whom (or why). Moreover, most participants defend this opacity as being essential to securing the most favorable prices for patients. This emphasis on the benefits of opacity contradicts prevailing wisdom in financial and many other markets, where opacity is seen as benefiting intermediaries and transparency as benefiting the public.

This brings us to another important difference. Prescription drug markets are dominated by three features not present in financial markets: stringent requirements for product safety and efficacy; product patent protection; and health insurance coverage for consumers’ purchases of medicines. The first of these, through the Food and Drug Administration regulations, has evolved into a complex and expensive system for testing new drugs before they can be marketed, all on the premise that market forces cannot sufficiently prevent releasing unsafe (or ineffective) drugs. Delays in that process can sometimes inhibit competition.

Patent protection for inventors, while considered essential to induce investment in new product development, also inhibits competition by providing exclusive marketing power to sellers. Further, insurance coverage for prescription drugs not only increases overall demand for products—potentially increasing prices even in competitive markets—but it also blunts people’s sensitivity to price increases, thus inviting sellers with patent protection to raise prices extensively. As insurance coverage expands, the potential for market forces to control product prices evaporates. At present, almost 90% of the costs of retail prescription drugs are covered by insurance. This further diminishes the ability of competition to “police” the market.

With these issues in mind, we believe that increased transparency has 2 vital roles in biopharmaceutical markets. First, it may increase the benefits of competition

by exposing noncompetitive arrangements and contracts. The “blame-the-others” rhetoric of various participants in the biopharmaceutical supply chain evokes the image of a circular firing squad. Unfortunately, the patient sits at the center of this process. Better information should end this unproductive behavior.

The second role of transparency would lay the groundwork for necessary regulation. Without improved understanding of how the various levels of the biopharmaceutical supply chain interact with one another, one cannot meaningfully know where regulation is needed in the absence of competition. Bringing light into the biopharmaceutical supply chain is a necessary step to improve our understanding, guiding future actions, and ultimately, increasing people’s health and well-being.

The views expressed in this article are those of the authors and not necessarily of the National Academies of Sciences, Engineering, and Medicine. ●

Additional Information:

The preceding article is based on an issue panel given at ISPOR 2018.

To view the author’s presentations, go to <https://www.ispor.org/conferences-education/conferences/past-conferences/ispor-2018/conference-presentations>

The Role of Real-World Data in Clinical Development

Manali Pendse, RWE, MA, Sciformix, a Covance Company, Maharashtra, India

KEY POINTS

.....
An increasing amount of electronic data is being generated in healthcare.
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Real-world data (RWD) are collected from a wide variety of sources to capture patient experiences during care.
.....

RWD and advanced analytics hold the promise to transform every aspect of clinical drug development.
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Healthcare is experiencing an avalanche of electronic data with sources that include social media, smart phones, activity trackers, electronic health records (EHRs), insurance claim databases, patient registries, health surveys, and more. Managing the wealth of available healthcare data allows health systems to create holistic views of patients, personalize treatments, improve communication, and enhance health outcomes. Collected outside of controlled clinical trials, RWD, has the potential to deliver vast amounts of insights into patient health and medical care. These insights can help create a full 360-degree view of patients to deploy personalized medications and also improve population health outcomes by tracking health trends and assisting in predicting upcoming developments. This article will give an overview of how RWD can influence the way clinical trials are designed and conducted today.

UNDERSTANDING THE IMPORTANCE OF RWD IN CLINICAL DEVELOPMENT

Randomized clinical trials (RCTs) are considered the “gold standard” in clinical development for establishing the safety and efficacy of an investigational product, because they are conducted in a way that helps remove as many sources of bias as possible from the process. RCTs operate in a controlled setting and are carefully planned to compare the safety and/or efficacy of the treatment (intervention) as compared to the control in a limited

from a wide variety of sources such as observational studies, retrospective database searches, case report form reviews, patient or disease registries, EHRs, and payers’ databases. These data are being increasingly obtained via electronic tracking systems used in healthcare to capture patient experiences during care.

Despite the extensive clinical research needed to get new medicines approved, it can still be hard to answer a patient’s basic questions about a drug. Is this the right medicine for me? Will I likely get the side effects they warn about? Patients often have different characteristics, experiences, and treatment protocols compared to the controlled environment of RCTs. Thus, it may not be possible to “generalize” the information gained from RCTs to broader groups of patients. Research conducted using RWD can help fill the gap between clinical trials and clinical practice, while properly analyzed RWD can provide key insights to help reduce medical costs, as well as improve safety and effectiveness profiles of drugs.

As pharmaceutical companies face the increasing challenges of ever more costly and complex clinical development, the combination of more accessible RWD and advanced analytics holds the promise to transform every aspect of clinical drug development. Furthermore, with advances in technology, it is now possible to analyze big datasets more efficiently. Statistical

Despite the extensive clinical research needed to get new medicines approved, it can still be hard to answer a patient’s basic questions about a drug. Is this the right medicine for me?

and homogenous population consisting of subjects with similar characteristics who are selected using precise inclusion and exclusion criteria. RCTs prioritize internal validity over the external validity.

Conversely, RWD collection occurs under normal day-to-day circumstances found outside of a typical RCT, and therefore, includes a much larger number of patients and patient types. RWD is collected

methods have also evolved, leading to greater confidence in deriving accurate inferences from these data. Retrospective data can serve as a source for determining the various patterns of the data, which are not usually seen during controlled RCTs. RWD can help determine the right patient population for a particular drug in order to arrive at the best outcomes. Even though the real-world studies aim for greater generalizability, there are some limitations.

For example, selection bias is a critical issue in real-world studies because patients are not randomized to treatment. This lack of randomization can produce situations in which treatment effectiveness is either under or overestimated, and also makes it difficult to avoid unmeasured confounding factors.

HOW CAN RWD HELP REDEFINE EXISTING CLINICAL DEVELOPMENT PRACTICES?

Real-world evidence (RWE), which is derived from the aggregation and analysis of RWD, can enable real-time protocol simulation, providing an opportunity to further examine study hypotheses before moving the investigational product into the clinical trial phase. This allows fine-tuning of clinical study protocols and more accurate selection of patient population for given clinical trials. The sponsors can validate opinions, assumptions, and historical experience by using RWD to back-test assumptions made in the clinical development plan. RWD can help in the selection of appropriate study endpoints including novel endpoints for testing both efficacy and safety of the investigational product, benefitting both the patients and providers. It may also help in identification of optimal trial duration, by calculating sample size using the actual background risk that takes into consideration trial-specific inclusion/exclusion criteria.

RWD can help in the clinical protocol feasibility assessment by providing insights into how stringent the inclusion and exclusion criteria are to determine patient eligibility. Using RWD to optimize the eligibility criteria can help accelerate patient recruitment and would ensure that obtained results are more broadly relevant. It will also provide guidance on how large (right size) and/or long (right duration) a study needs to be to allow a test drug to demonstrate a significant impact on disease outcomes.

By utilizing RWD, it is possible to identify the appropriate group of patients to enroll in a RCT and define who would or would not respond well to a particular drug or therapy. For example, one of Amgen's cancer therapies gained its first regulatory approval based on a single-arm phase II study supported by RWE obtained from medical records [1]. The company did not include a traditional standard-of-care comparator arm in the study because the patients enrolled in the study had already failed to respond to standard therapies based on RWE.

In another study, published in the *American Journal of Cardiology*, findings suggested that patients with atrial fibrillation (AF) may benefit from a structured weight reduction program [2]. Such findings from real-world studies (RWS) can be used to identify covariates to be included while modeling clinical trial data or to fine-tune the subgroups that are used and analyzed in RCTs.

As part of a US multisite prospective registry of patients with AF, researchers analyzed 3 years of data (2013-2016) and found that 13% were not treated with the recommended doses. In addition, 6% of registry patients were not included in this study because renal function was not checked during the 1-year follow-up, which was another deviation from the package insert recommendations. Such insights can be useful to determine specific aspects to be considered during clinical trial conduct to ensure required dosing and minimize deviations.

RWD, along with new models and analytics, helps to identify high performing sites and investigators based on quality, prior performance, participation and data delivered in previous studies. This is critical information to identify the right sites to reach the target number of patients. RWD and site-specific data on existing and available patients helps plan the recruitment at sites. This eliminates the risk of over committing and under delivering on recruitment. Utilizing EMRs (electronic medical records) can double enrolment rates, which can lead to 30% reduction in trial enrolment costs.

Clinical development programs can be substantially strengthened by use of RWD. The Salford Lung Study (SLS) is an example of this and is the world's first digitally enhanced RCT. The data provided by SLS complement the existing data provided by the conventional RCTs [3]. A pragmatic trial such as SLS, which enrolled patients in an everyday clinical practice setting who would often be excluded from a traditional RCT, would especially benefit from use of RWD in designing the trial. For example, SLS included patients who are concomitantly being treated for other chronic diseases. RWD about concomitant conditions and treatments would aid in granular definitions of inclusion and exclusion criteria, requirement for stratified sampling, subgroup analyses, and more.

SUMMARY

RWD has already started changing the way clinical trials are being conducted. RWD has the potential to provide evidence for expanding the approved uses of a drug to new types of patients and new diseases as well as identifying populations of patients whose needs aren't being met by current therapies. The evidence can be used to support investments in clinical studies to gain approval for new indications. The combined use of RWD, statistical analysis, machine learning, and predictive modelling will likely change the face of clinical development in the coming years with the promise of streamlining drug development processes, improving speed to market and reducing costs. ●

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Q&A

The “Patient Journey” to Real-World Evidence: An Interview With Tanisha Carino

Value & Outcomes Spotlight's had the chance to sit down with Tanisha Carino, PhD, a respected senior executive with more than 2 decades of experience in academia, government, and the private sector, to gain a further understanding on the 21st Century Cures Act. She joined the Milken Institute in January 2018 as executive director of *FasterCures*, the center devoted to saving lives and improving the medical research system. Throughout her distinguished career, including GlaxoSmithKline, Avalere Health, and Medicare, Carino has been at the forefront of collaborative efforts to promote policies, research, and business practices that support the fight against disease and improve the lives of patients. Carino earned her PhD in health policy from Johns Hopkins University.

FasterCures, a Center of the Milken Institute, has a singular goal: to save lives by speeding science to all patients. For over 15 years, *FasterCures* has created a global community dedicated to accelerating medical solutions and has worked with leaders across biomedical research to accelerate medical research, including the passage of 21st Century Cures.

***Value & Outcomes Spotlight:* How do you feel about our progress over the past 4 to 5 years in incorporating the patient voice into real-world evidence?**

Tanisha Carino: While the promise of “big data” has existed for some time, figuring out how to harness it to impact patient outcomes has come of age with the advent of new tools, data sources, and ever-increasing patient engagement and stakeholder collaboration.



The rise of social media and advancements in digital health have connected and empowered patients to a level not seen in the past. This has led to an explosion of patient-generated data from an ever-expanding number of sources that offer not only new (sometimes continuous) data streams, but additional opportunities to engage patients and understand their perspectives, goals, and needs.

For example, this month we see the US Food and Drug Administration (FDA) turning to its Patient Engagement Advisory Committee for suggestions from patients on how the agency can leverage patient-driven platforms to better engage patients and collect real-world data. Digital health has brought new stakeholders to the table and is revolutionizing the way that data are collected, shared, and used, as well as changing patient care.

We are seeing increased collaboration to address the myriad challenges and uncertainties regarding how to best collect and utilize data for each intended use. Strides are being made in integrating data sources, developing standards, and identifying how to engage patients meaningfully and collect patient-generated data to help make medical product development more efficient and less burdensome for patients and to better align products with patient needs.

What are your thoughts on incorporation of the patient voice in clinical research design and real-world data collection—are things progressing there, too?

It is an exciting time in real-world data and evidence development, particularly as it relates to including patient perspectives in the

decision-making process of medical product development and delivery. We have the opportunity, with the scale-up of electronic health records and other types of digitally collected data, to have a more complete picture of patients' experiences of their disease or condition, as well as their treatments and care.

Practically speaking, we continue to struggle with some difficult issues—poor data quality and lack of data standardization make it challenging to derive meaningful insights, siloes remain among different types of data that could be relevant to patients, like their wearable data. Additionally, the differences between patient data generated in the controlled process of a clinical trial and data generated in the real-world context are challenging to interpret (statistical significance versus clinical meaningfulness). However, progress has been made toward tackling challenges related to data aggregation, through the PCORI-funded Clinical Data Research Networks and standardization of outcomes that matter to patients through the development of core outcome sets.

Strides are being made in integrating data sources, developing standards, and identifying how to engage patients meaningfully and collect patient-generated data to help make medical product development more efficient and less burdensome for patients and to better align products with patient needs.

One critically important next step to ensure that momentum continues—and we can realize the promise of turning patient journeys into data—is to directly engage with patients and caregivers. Patient engagement requires a certain level of know-how in terms of patients understanding what comprises their health data, how they are being used to improve their care and drive research, and how they can be actively engaged in contributing their data, and their time, as part of their participation in research. Efforts are underway to support patient communities, including our Health Data Basics project as well as a newly created effort in the United Kingdom called Understanding Patient Data.

When you consider what is possible relative to that which is practical, how do you see “Cures” supporting better evidence development by incorporating the patient voice into real-world data?

We are currently seeing how 21st Century Cures has raised the importance of partnering with patients and how it will ultimately raise the profile of those organizations investing in early pilot projects to incorporate the patient voice in evidence generation using real-world data. Through requirements mandated by Cures, including issuing guidance on Patient-Focused Drug Development, the FDA is setting expectations for industry. In addition, as the patient experience section in the medical product label becomes populated with data, it will be interesting to see how that information is communicated to patients and providers, as well as used by decision makers in health care.

At the same time, patient organizations continue to function as critical partners in evidence development, from their support

of basic and translational research and funding of natural history studies, to the establishment of patient registries and master protocols. However, these efforts require a high level of resources, and a need exists to support capacity building of these organizations, to engage more broadly and, for some, to collect and generate patient data.

What do you see as the next steps for the patient perspective propelling a data-driven journey moving forward?

The next steps exist at several levels and will require engagement from individuals, communities, and organizations.

First, patient groups play a critical role in both advocating for the unmet needs in their patient communities and catalyzing research and partners in data collection and decision making.

As patient groups play a bigger role across the ecosystem, they are determining their assets and resource needs, so being focused and strategic is critical. If we are truly going to leverage big data to accelerate research, we must include individual patients, caregivers, and patient communities in the generation and interpretation of the data to ensure that the evidence generated is important to them and serves their unmet needs.

This will take scaling up patient engagement efforts through the redesign of clinical trials to allow for virtual participation, integrating wearable and other types of data generated by patients, and building the knowledge and empowerment of patients to be more active participants with their health data.

Second, as part of their efforts to drive innovation in medical research, patient organizations can take greater latitude with the types of data they collect, data that traditional clinical research and outcomes research community view as “messy”—sleep, diet, activity level, and even shopping patterns. However, health and how we measure it require not only traditional clinical outcomes of interest, but also data on the true lived experience. More needs to be done to create a stronger bridge between research and patient communities that support collaboration, shared language, and advancing analytical methods.

Finally, decision making is in flux because the data used to make decisions are evolving, so gathering stakeholders from across the ecosystem to define what data have value for what types of decisions is a critical next step. ●

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