

NOVEMBER/DECEMBER 2020 VOL. 6, NO. 6

VALUE & OUTCOMES SPOTLIGHT

A magazine for the global HEOR community.



CHALLENGES IN PRECISION MEDICINE:

AIMING TO ALIGN DATA,
VALUE, AND COSTS

- 4 HEOR COMPETENCIES
- 11 REGULATORY DECISIONS FOR MEDICAL DEVICES
- 30 TIME FOR A CHANGE IN DRUG PRICING
- 42 MAKING AN IMPACT: ISPOR TASK FORCE REPORTS

VALUE & OUTCOMES SPOTLIGHT

NOVEMBER/DECEMBER 2020
VOL. 6, NO. 6

TABLE OF CONTENTS

EDITORS-IN-CHIEF

Zeba M. Khan, RPh, PhD
Laura T. Pizzi, PharmD, MPH

ASSOCIATE EDITORS

Murtuza Bharmal, PhD, MS
Benjamin Craig, PhD

EDITORIAL ADVISORY BOARD

Soraya Azmi, MBBS, MPH
(United States)

Agnes Benedict, MSc, MA
(United Kingdom)

Karin Groothuis-Oudshoorn, PhD
(The Netherlands)

Yvonne Lee YL, PhD, MPH
(Singapore)

Martin Marciniak, PhD
(United States)

George Papadopoulos
(Australia)

Louise Parmenter, PhD, MSc
(United Kingdom)

Marisa Santos, PhD, MD
(Brazil)

Stephen W. Schondelmeyer, PhD
(United States)

Mondher Toumi, MD, PhD, MSc
(France)

.....

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.

FROM THE EDITORS

- 3 2020: We Have Prevailed!

ISPOR CENTRAL

- 4 ISPOR Speaks
ISPOR HEOR Competency Framework
Jim Murray and Laura Pizzi
- 6 HEOR News
- 8 Research Roundup
- 10 From the Journals
- 11 From the Patients
Using Patient Preference Information in Medical Device
Regulatory Decisions
- 15 From the Regions
HTA to Support Universal Health Coverage in Asia Pacific
- 18 ISPOR Awards
- 21 Conferences

FEATURE

- 24 Challenges in Precision Medicine: Aiming to Align Data, Value, and Costs
- 29 By the Numbers: Global Perspectives on Precision Medicine

HEOR ARTICLES

- 30 Time for Change? Has the Time Come for the Pharmaceutical Industry to Accept Modest Prices?
- 33 The Evaluation of Pivotal Trials for Advanced Therapies From Regulatory and Health Technology Assessment Perspectives in Europe
- 37 Regulatory Pathways in Europe, the United States, and Japan and Health Technology Assessments for Gene Therapies

Q&A

- 42 How to Make an Impact on Healthcare Decision Making?
An Interview With Marc L. Berger, MD

EDITORIAL STAFF

Lyn Beamesderfer

Director, Publications
lbeamesderfer@ispor.org

Margaret M. Rafferty

Manager, Publications
mrafferty@ispor.org

Jennifer A. Brandt

Editorial Assistant
jbrandt@ispor.org

ISPOR CORPORATE OFFICERS

Nancy S. Berg

Chief Executive Officer/
Executive Director

Sue Capon

Chief Operations Officer

Richard J. Willke, PhD

Chief Science Officer

Lucinda Orsini, DPM, MPH

Associate Chief Science Officer

Betsy Lane

Director and Chief Marketing
& Communications Officer

ISPOR HEADQUARTERS

505 Lawrence Square Blvd, S
Lawrenceville, NJ 08648
Tel: 609-586-4981
Fax: 609-586-4982
info@ispor.org
www.ispor.org

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

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

Published bi-monthly by:
ISPOR
505 Lawrence Square Blvd, S
Lawrenceville, NJ 08648 USA

Direct photocopy permission and reprint
requests to Director, Publications.

© 2020 ISPOR—The professional society for health
economics and outcomes research.

*While Value & Outcomes Spotlight is designed
to provide accurate information regarding the
subject matters covered, the views, opinions, and
recommendations expressed, are those of the
contributors and not of the International Society for
Pharmacoeconomics and Outcomes Research (ISPOR).*

FROM THE EDITORS

As 2020 draws to a close, the past year has seen many remarkable accomplishments in the health economics and outcomes research (HEOR) field. Let's face it—2020 has been a difficult and challenging year and many of us are hoping that 2021 will usher in a resolution to the COVID-19 pandemic, as well as find successful means for addressing the many sociopolitical issues that also plague our world. As a discipline, we have so much of which to be proud. During these challenging times, our scientists have remained dedicated to conducting cost and outcome evaluations while health technology assessment bodies have continued to inform global value-based decisions on drugs and devices. We have seen revolutionary advancements in precision medicine and digital health and are applying our methods to add even more value to these game-changing innovations. We have continued to promote real-world evidence (RWE), aggressively sought increases in database size and scope that are essential for conducting quality RWE studies, and developed machine learning methods to better analyze and act upon RWE in real time.

When the world most needed us, we have risen to the occasion to develop epidemiological and economic models of COVID-19. We used our methods to better understand the value of basic public health strategies against a deadly pandemic—social distancing, contact tracing, and handwashing—as well as to begin to evaluate the potential cost-effectiveness of vaccines and antiviral treatments. As just one example, we highlight in this issue a study employing a discrete choice experiment to better understand Americans' willingness to accept the tradeoffs of social distancing by measuring their preference for public health benefits over economic hardship.

During this challenging time, we have also continued to connect with each other through the ISPOR Annual Meeting that was converted to a virtual, digital platform in warp speed and was followed by the virtual Asia Pacific and European conferences. Although nothing replaces in-person networking, we have accepted Zoom as the next-best option for staying connected. For the first time, we provided news coverage of these conferences with the indispensable help and creativity of *Value & Outcomes Spotlight's* talented editorial staff and ISPOR's student members. We continued to build and advance our competencies and the competencies of others through Short Courses, Special Interest Groups, Task Forces, and the ISPOR Competency Framework that maps the knowledge and skills needed for successful HEOR professionals.

Through our unique and steadfast contributions, our accomplishments reveal to us an endurance, creativity, and drive that will beacon HEOR through even the most challenging times. If we can accomplish as much during a global pandemic and recession, then certainly 2021 holds equal promise! ISPOR needs us, our colleagues need us, HTA authorities need us, payers need us, biopharma needs us, students need us, and, most importantly, patients need us more than ever—for this year and many more years to come!

We have prevailed!

Zeba M. Khan, RPh, PhD and
Laura T. Pizzi, PharmD, MPH
Editors-in-Chief,
Value & Outcomes Spotlight



ISPOR SPEAKS

The ISPOR HEOR Competency Framework™

Jim Murray, PhD and Laura T. Pizzi, PharmD, MPH

Health economics and outcomes research (HEOR) has expanded globally, fueling demand for professionals trained in the discipline. This has different implications for the diverse ISPOR membership; life science companies need to find and recruit talent with the right training and experience, while students and faculty need to understand what skills companies seek to be able to tailor their educational pursuits to meet this demand. These needs, among others, gave rise to the ISPOR Competency project, which has established a set of competencies for HEOR professionals. The 41 competencies are organized into 13 topic domains (Table 1) that collectively comprise the ISPOR Health Economics and Outcomes Research Competencies Framework™, which was recently published in *Value in Health*.¹ The Framework represents an important accomplishment for ISPOR and for our discipline as a whole.

The surveys yielded rich results. The general ISPOR membership survey revealed the importance of each competency to the HEOR discipline as well as the relevance of each competency to the job held by the respondent.

The Framework is a product of collaboration between the ISPOR Institutional and Faculty Advisor Councils, which developed an initial list of competencies that were then validated by 3 independent assessments. First, we used a natural language analysis to examine overlap between the competencies included in ISPOR Career Center HEOR job postings and to

identify missing competencies. Next, we obtained qualitative input from a focused Institutional Council–Faculty Advisor Council reactor panel. The final step was a set of surveys collected from faculty members, student members, and ISPOR membership at large (which we refer to as the “general membership”).

The surveys yielded rich results. The general ISPOR membership survey revealed the *importance* of each competency to the HEOR discipline as well as the *relevance* of each competency to the job held by the respondent. All competencies (except Pharmacovigilance Analysis) were rated as important or *critically important* by a significant majority of respondents. We retained this competency, although it's not core to HEOR, and anticipate that future work will elucidate whether it should be retained in the Framework.

General membership survey results also indicated that respondents felt all competencies were *relevant* to their jobs, except Pharmacovigilance Analysis and Career Development – Academia, which may not have been sufficiently represented by the job types held by respondents. In addition, from the general membership survey, we found that 7 specific HEOR specialty tracks covered 80% of the respondents. These were:

- HEOR Generalist (health economics and health outcomes research)
- Health Economist
- HEOR Management or Administration
- Health Technology Assessment
- Real-World Evidence and Observational Study Specialist
- Patient-Reported Outcome/Clinical Outcomes Assessment
- Pricing, Access, and Reimbursement

As expected, we found the relevance of competencies to differ based on specialty track.



The faculty member survey assessed the extent to which their university's HEOR graduate degree programs covered each of the competencies. The faculty results were then compared to the student member survey that assessed students' exposure to each of the competencies in their HEOR academic program. There was strong agreement between the students' exposure to the competencies and the degree to which they were covered in the academic programs we surveyed.

After completing the surveys, we aligned the resulting competencies and domains with a taxonomy of education topics created by the ISPOR Education Council. The objectives of this task were to: 1) ensure that ISPOR short courses can be mapped into the ISPOR Competency domains, and 2) facilitate the ability of short-course participants to map their learnings to the competencies.

Now that the Framework has been established, we have received tremendous interest in using it as a tool to inform both individuals and organizations interested in gaining or assessing HEOR competencies. The ISPOR Student Network has used it to identify webinar topics to present to membership worldwide; New Professionals are using it to understand what competencies are covered by HEOR fellowships; institutional members are using it to identify what competencies they seek in company hires; faculty are using it to assess what competencies their programs cover and/or what niche their program has; and complementary disciplines, such as medical affairs, have taken interest in understanding what HEOR competencies apply to professionals in their discipline.

As interest takes hold, we have embarked on the key next steps towards refining the Framework. This entails dissecting the broadest competencies into detailed topics—starting with competency 10.1 Statistics and Analytics. As a cornerstone of HEOR, this particular competency certainly requires greater specificity to be most useful. The effort is being led by Ebere Onukwugha, PhD, and involves assessment of methodological writings, reports, and training programs related to HEOR analytics and engagement of ISPOR experts on the topic. Ongoing work also involves identifying permutations of the Framework that are specific to each HEOR specialty track. Indeed, we see the ISPOR Competency Framework as a dynamic entity that should evolve with the HEOR discipline.

ISPOR member input has been instrumental to this initiative and will continue to play a critical role moving forward. Feel free to provide your suggestions and ideas by contacting us via email at murray_james@lilly.com or laura.pizzi@rutgers.edu •

Reference

1. Pizzi LT, Onukwugha E, Corey R, Albarmawi H, Murray J. Competencies for professionals in health economics and outcomes research: The ISPOR Health Economics and Outcomes Research Competencies Framework. *Value Health*. 2020;23(9):1120-1127.

Table 1. The ISPOR Health Economics and Outcomes Research Competencies Framework™

1. BUSINESS MANAGEMENT
1.1 Business Acumen
1.2 Pricing, Reimbursement, and Access
1.3 Marketing and Market Research
1.4 Business Operations, Including the Business Planning Process
1.5 Assessment and Management of Vendors
2. CAREER DEVELOPMENT
2.1 Orientation Towards Solutions and Success
2.2 Career Development — Academia
2.3 Career Development — Industry, Government, and Other Settings
3. CLINICAL OUTCOMES
3.1 Drug Development Expertise
3.2 Clinical and Medical Expertise
4. COMMUNICATION AND INFLUENCE
4.1 Scientific Medical Writing
4.2 Presentation Development and Delivery
4.3 Executive Communications
4.4 Teamwork, Team Dynamics, and Relationships
5. ECONOMIC EVALUATION
5.1 Burden of Illness Analysis
5.2 Economic Analysis Alongside Clinical Trials
5.3 Health Economic Modeling
6. EPIDEMIOLOGY AND PUBLIC HEALTH
6.1 Epidemiology, Including Pharmacoepidemiology Studies
6.2 Pharmacovigilance Analyses
7. HEALTH POLICY AND REGULATORY
7.1 Health Policy and External Environment Expertise
7.2 Fundamentals of Health Insurance: Design, Coverage, and Pricing
7.3 Regulatory Activity and Review
8. HEALTH SERVICE DELIVERY AND PROCESSES OF CARE
8.1 Customer Interactions and Relationships
8.2 Health System Expertise (Regional and Affiliate Level) at the Payer Level
8.3 Program Evaluations
9. HEALTH TECHNOLOGY ASSESSMENT
9.1 Global Understanding of Health Systems and HTA
9.2 Health Technology Assessment (HTA) Evidence Requirements and Development
9.3 Product Dossier (Global and Local)
9.4 Decision Analysis
10. METHODOLOGICAL AND STATISTICAL RESEARCH
10.1 Statistics and Analytics
11. ORGANIZATIONAL PRACTICES
11.1 Bioethics and Human Subjects Rights and Protections
12. PATIENT-CENTERED RESEARCH
12.1 Patient-Reported Outcomes (PRO) Development, Including Psychometrics
12.2 Utility and Quality of Life Studies
12.3 Qualitative Research
13. STUDY APPROACHES
13.1 Clinical Trial Design and Implementation
13.2 Pragmatic Studies
13.3 Prospective and Retrospective Observational Studies (Real-World Evidence)
13.4 Retrospective Claims Database Studies
13.5 Patient Registries, Including Risk Evaluation Monitoring Studies
13.6 Systematic Literature Reviews
13.7 Meta-analysis and Indirect Comparisons

HEOR NEWS

1 Surprise Federal Drug Rule Directs Insurers to Reveal What They Pay for Prescription Drugs (Kaiser Health News)

Under an unexpected new Trump administration rule, insurers will have to give their customers estimated out-of-pocket costs for prescription drugs and disclose to the public the negotiated prices they pay for drugs. The rule is part of a broader rule issued in October that forces health plans to disclose costs and payments for most healthcare services. The drug price rule, which was promoted as a way to encourage competition and empower consumers to make better medical decisions, does not apply to Medicare or Medicaid.

[Read more.](#)

2 Indication-Based Pricing Sparks Interest in the United Kingdom (Pink Sheet)

A cross-sector experts panel recommends tying benefits of a drug to the benefits that it delivers, as well as setting different prices for different indications treated by a drug. The panel aims to improve patient access to innovative new cancer indications.

[Read more.](#)

3 Estimation of Differential Occupational Risk of COVID-19 by Comparing Risk Factors With Case Data by Occupational Group (*American Journal of Industrial Medicine*)

In a study published in the November 18 issue of the *American Journal of Industrial Medicine*, Dr Michael Zhang looked at a way to assess the differential risk of various professions of developing COVID-19. By using predictors from the Occupational Information Network (O*NET) database and correlating them with case counts published by the Washington State Department of Health, Zhang found 2 variables that correlate with case prevalence: disease exposure ($r = .66$; $P = .001$) and physical proximity ($r = .64$; $P = .002$), and predict 47.5% of prevalence variance ($P = .003$) on multiple linear regression analysis.

[Read more.](#)

4 IQVIA Joins FDA to Advance COVID-19 Understanding at Community Level Through COVID Active Research Experience (CARE) Project (IQVIA)

To understand the impact of COVID-19 on people—what symptoms individuals experience, the length and severity, and whether any medications or vitamin supplements they are taking affect the severity of their coronavirus symptoms—IQVIA and the US Food and Drug Administration (FDA) have started a joint program that will use data from IQVIA's CARE Project registry. The registry was started in April and is open to US-based residents who think they may have been exposed to the coronavirus, regardless of whether they have been diagnosed with COVID-19, including people who have continued with everyday life and may have been exposed. Working with the FDA, IQVIA's scientific team will use the ongoing CARE Project to

provide rapid insights into important COVID-19 questions that have yet to be explored or answered well via other available real-time data.

[Read more.](#)

5 Syneos Health on Digital Therapeutics and Payers (Syneos Health)

Looking back at this panel from June, Syneos Health presents research that shows how payers are concerned with the real-world utility of digital therapeutics, a market that has grown more than 50% in the past 3 years. The panel also covered existing pricing and payment models and existing case studies.

[Read more.](#)

6 Vertex Pharma's Vision for Reimbursement Innovation (Pharmaphorum)

Pharmaphorum's Paul Tunnah talks with Simon Lem, regional vice president for Northern Europe and Australia for Vertex. Lem, who had led the digital launch of Vertex's novel cystic fibrosis drug, Kaftrio (ivacaftor/tezacaftor/elexacaftor), describes how Vertex tried to meet the needs of the cystic fibrosis patient population (that tends to be young and tech-savvy) and his hopes that the speedy nature of the Kaftrio approval by the National Health Service is a good signal for the future of reimbursement.

[Read more.](#)

7 A Leading Artificial Intelligence Researcher Calls for Standards to Ensure Equity and Fairness (STAT News)

The old computing adage regarding programming and the quality of results was GIGO, or "garbage in, garbage out." When it comes to programming artificial intelligence (AI) engines to review health information, that acronym could be updated to RIRO, or "racism in, racism out." Regina Barzilay, a top AI researcher at the Massachusetts Institute of Technology, warns that AI systems developed for medicine must become more transparent and judged against a set of common standards to ensure equity and fairness. These engines must be trained on diverse populations to be able to provide more equitable care, she says.

[Read more.](#)

8 ICER Provides Second Update to Pricing Models for Remdesivir as a Treatment for COVID-19 (ICER)

The Institute for Clinical and Economic Review (ICER) in November issued a second update to its pricing model for the drug. The group stated that an analysis of 4 studies shows that the evidence no longer supports an assumption of survival benefit from remdesivir. With the new analysis, ICER suggests a health-benefit price benchmark of \$2470 for hospitalized patients with moderate-to-severe disease, and \$70 for patients hospitalized with milder disease.

[Read more.](#)

9 To Maintain Opioid Sales, Purdue Was Advised to Pay Rebates to Health Insurers for Each Overdose

(Pharmalot)

In perhaps not the best look for the company, consultants, or for health insurers, court documents showed that Purdue Pharma was advised by McKinsey to pay a rebate of up to \$14,000 to its 7 top health insurers for each patient that overdosed on OxyContin. It is not clear that Purdue ever implemented the move, which was suggested to maintain “crucial business relationships” as the company faced serious challenges to OxyContin sales. It had projected that it could cost the company \$3 million to \$15 million a year. The disclosure came in the wake of a decision by a US bankruptcy court judge who approved an \$8.3 billion settlement between Purdue and the Justice Department.

[Read more.](#)

10 How Professionals Are Working to Address Healthcare Disparities in Northeast Ohio (WKYC)

The Center for Community Solutions studied Ohio neighborhoods and found a disparity of 23 years between the highest life expectancy neighborhood and the lowest life expectancy neighborhood. Additionally, systemic racism is fact beyond socioeconomic status, with Blacks having higher education and incomes still experiencing health disparities. In response, Cleveland Clinic set up programs to help educate and then hire future nurses as well as other critical positions.

[Read more.](#)

11 “All-Hands-on-Deck” Approach Needed on Social Determinants of Health (American Medical Association)

An AMA Council on Medical Services report has found that social determinants of health need to be addressed not in the traditional ways by stakeholders in the healthcare system. Health plans, for example, should design benefits and coverage to cover the nonmedical but critical things patients need. And public and private health plans should examine implicit bias and the role of racism and social determinants of health, including through such mechanisms as professional development and other training.

[Read more.](#)

12 You Can Influence ICER Recommendations, You Just Need the Right Evidence (Panalgo)

According to Matt Sussman at the healthcare analytics company Panalgo, it is possible to influence ICER recommendations if a pharmaceutical manufacturer can provide cost-effectiveness models developed by outside groups. The reason is that the results of these budget impact analyses are often more favorable than the “base” ICER ones.

[Read more.](#) •

RESEARCH ROUNDUP

Section Editor: **George Papadopoulos, BSc(Hons)**, GradDipEpi, MAICD Partner & Director, Lucid Health Consulting & School of Medicine, UNSW, Sydney, NSW, Australia

The articles in this session of Research RoundUp look at precision medicine. Quite the topic! Precision medicine has held promise for many years as a tailored approach to both disease prevention and treatment that considers the differences in people's genetic makeup. Genomic sequencing underpins the value of precision medicine in being able to better predict, prevent, diagnose, and treat diseases. There are more than 750 trials of cell and gene therapies in almost 30,000 patients underway globally as of June 2020, and cell and gene therapies products account for approximately 12% of the pharmaceutical industry's clinical pipeline. There is an abundance of literature on precision medicine and in this issue, and we have tried to identify recent research that encapsulates these characteristics and is worth reading.

Precision Medicine: Steps Along the Road to Combat Human Cancer

Nassar SF, Raddassi K, Ubhi B, Doktorski J, Abulaban A. *Cells*. 2020;9(9):2056. <https://doi.org/10.3390/cells9092056>.

Summary

The authors examine the recent innovations in assays, devices, and software, along with next-generation sequencing in genomics diagnostics that are in use or are being developed for personalized medicine. They begin with a discussion of the lessons learned to date and the current research on pharmacogenomics. The authors take us on a journey from the ancient Chinese, Greek, Roman, and Arabic theories that sought to answer fundamental questions of how and why some individuals either developed or avoided diseases and conditions all the way through to the Human Genome Project and onto the 21st century. In this comprehensive review, the topics explored the benefits of personalized medicine, the progression of precision medicine and positive outcomes, the challenges facing precision medicine, pharmacogenetics and pharmacogenomics, review of technologies and recommendations, and a conclusion of the future promise of precision medicine. The authors also provide a section of examples of precision medicine drugs.

Relevance

If you don't read past this first article, then this article will fully ground you in what precision medicine is and its impact now and into the future. Great progress is being made in fighting cancer and the ability to discern, record, and analyze genetic information provides the means to rapidly detect cancer and other diseases earlier and more accurately than ever before and that is the true global perspective on precision medicine.

Health Economics Tools and Precision Medicine: Opportunities and Challenges

Veenstra DL, Mandelblatt J, Neumann P, et al. *Forum Health Econ Policy*. 1998;23(1):20190013. <https://doi.org/10.1515/fhep-2019-0013>.

Summary

Health economics frameworks and tools can elucidate the effects of legal, regulatory, and reimbursement policies on the use of precision medicine while guiding research investments to enhance the appropriate use of precision medicine. This review provides an overview of precision medicine and key policy

challenges for the health economics field; explains the potential utility of economics methods in addressing these challenges; describes recent research activities; and summarizes opportunities for cross-disciplinary research. To accomplish this, the authors selected key examples to discuss based on the potential utility of economic approaches for informing precision medicine analyses and policies, and with the intention of helping health economists not currently working in precision medicine understand the applicability of current economics tools in this area.

Relevance

Precision medicine is evolving at a tremendous pace and this paper provides an overview of the promise of precision medicine and the implications of precision medicine for improved health economics. Examples of the application of economic tools to precision medicine highlight opportunities for economics in precision medicine, as well as important challenges. There are a multitude of economics tools that can be applied to precision medicine to better understand potential benefits, harms, and economic impacts. This paper is worth reading many times over.

Targeting DNA Damage Response and Replication Stress in Pancreatic Cancer

Dreyer SB, Upstill-Goddard R, Paulus-Hock V, et al. *Gastroenterology*. 2020;1-16. <https://doi.org/10.1053/j.gastro.2020.09.043>.

Summary

Pancreatic ductal adenocarcinoma, the more common form of pancreatic cancer, is dominated by mutations in 4 well-known cancer genes (*KRAS*, *TP53*, *CDKN2A*, and *SMAD4*). Only a few genes are mutated in 5%–15% of cases, amidst an ocean of infrequently mutated genes in the majority of patients. This diversity may explain the lack of progress with targeted therapies, because actionable genomic events being targeted therapeutically are present in only a small proportion of unselected participants in clinical trials. The research builds on previous work on DNA damage-response deficiency, which is a hallmark of cancer—including pancreatic cancer—and aims to expand the indications for novel DNA damage-response inhibitors beyond patients with defects in homologous recombination mechanisms. The aim was to refine proposed DNA damage response biomarkers of platinum response to be tested in prospective clinical trials and to correlate and overlap

this with cell-cycle inhibitor response to identify patients who will respond to novel agents, such as ataxia-telangiectasia Rad3-related and WEE1 inhibitors.

Relevance

This study will end up being a landmark paper. Based on preclinical models of patient-derived cell lines of pancreatic cancer and organoid responses that were generated from patients with pancreatic cancer to develop new molecular markers that can predict who will respond to drugs targeting DNA damage, the findings mark an important step for potential treatment options for pancreatic cancer, improving the options and outcomes for a disease where survival rates have remained the lowest in oncology. This paper highlights the basic and translational research required to enable biomarker-driven clinical testing and allows refinement of biomarkers predicting meaningful responses and potential translation into clinical practice.

The Egyptian Collaborative Cardiac Genomics Project: Defining a Healthy Volunteer Cohort

Aguib Y, Allouba M, Afify A, et al

npj Genom Med. 2020;(5):46.

<https://doi.org/10.1038/s41525-020-00153-w>

Summary

Cardiovascular disease is a major cause of death and disability worldwide, and its prevalence continues to increase in low- and middle-income countries toward epidemic proportions. The Egyptian Collaborative Cardiac Genomics (ECCO-GEN) Project is recruiting 1000 Egyptian healthy volunteers from the general population who consent to be recalled to future research and are simultaneously establishing a regional biobank that hosts a broad range of biological samples for prospective studies. Participants are fully phenotyped with respect to cardiovascular health. The full dataset of 1000 volunteers will aid in distinguishing between incidental and medically actionable variants, and thus enhance diagnostic and treatment strategies. All individuals underwent detailed clinical investigation, including cardiac magnetic resonance imaging, and were sequenced using a targeted panel of 174 genes with reported roles in inherited cardiac conditions.

Relevance

The ECCO-GEN project aims at defining the genetic landscape of an understudied population and providing individual-level genetic and phenotypic data to support future studies in cardiovascular disease and population genetics.

Returning Results in the Genomic Era: Initial Experiences of the eMERGE Network.

Wiesner GL, Kulchak Rahm A, Appelbaum P, et al

J Pers Med. 2020;10:30.

<https://doi.org/10.3390/jpm10020030>

Summary

The electronic Medical Record and Genomics (eMERGE) Network is addressing the implementation of genomic medicine within the US healthcare system. Established more than 10 years ago, the primary goal of the network has been “to develop,

disseminate, and apply approaches to research that combine biorepositories with electronic medical record systems for genomic discovery and genomic medicine implementation research. There is currently no protocol or practice standards for returning unsolicited genetic tests that are identified as a consequence of clinical care or research programs. eMERGE3 emulates the “real world” of genomic medicine today, in which organizations are independently exploring incorporation of genomics into clinical practice and provides an ideal setting to study the return of results (RoR) processes for genomic sequence results that were not solicited by healthcare professionals (HCPs) in a diverse set of healthcare institutions. This paper describes the planned RoR processes independently developed at each of the 10 eMERGE3 sites and examines the similarities and differences in approaches for the disclosure of unsolicited genomic results to participants and their HCPs in order to identify “best practices” for the utilization and return of genomic information within the healthcare system today.

Relevance

This report on initial ROR processes and experiences across 10 eMERGE3 sites highlights the current real-world needs of healthcare systems in developing new pathways to support genomic medicine. The paper provides a foundation for studying within eMERGE3 and other future studies the impact of these RoR processes on patient, provider, and organization utilization of genomic information.

Drug Use in Denmark for Drugs Having Pharmacogenomics (PGx) Based Dosing Guidelines From CPIC or DPWG for CYP2D6 and CYP2C19 Drug–Gene Pairs: Perspectives for Introducing PGx Test to Polypharmacy Patients

Westergaard N, Søgaard Nielsen R, Jørgensen S, Vermehren C

J Pers Med. 2020;10(1):3.

<https://doi.org/10.3390/jpm10010003>

Summary

The cytochrome P450 drug metabolizing enzymes CYP2D6 and CYP2C19 are the major targets for pharmacogenomics testing and determining for drug response. Clinical dosing guidelines for specific drug–gene interactions are publicly available through PharmGKB in Denmark. The aim of this register study is to map the use of drugs in Denmark for drugs having actionable dosing guidelines, ie, dosing recommendations different from standard dosing for CYP2D6 or CYP2C19 drug–gene interactions in terms of consumption. The aim of the study was to map the use of drugs in Denmark by applying Anatomical Therapeutic Chemical codes for drugs having dosing guidelines (CPIC or DPWG) for CYP2D6 and/or CYP2C19, in terms of consumption of defined daily dose.

Relevance

This research underscores the importance of accessing and accounting for drug–drug interactions, drug–gene interactions, and drug–drug–gene interactions while understanding that it is a complex process demanding multidisciplinary collaborations to obtain infrastructural capacities for good decision-making processes, as well as further studies to assess the economic impact of pre-emptive pharmacogenomics panel testing. •

FROM THE JOURNALS

Looking at Reluctant Americans and Coronavirus-Related Restrictions

Section Editors: Soraya Azmi, MBBS, MPH, Beigene, USA; Agnes Benedict, MSc, MA, Evidera, Budapest, Hungary

Willingness to Accept Trade-Offs Among COVID-19 Cases: Social Distancing Restrictions and Economic Impact

Shelby Reed, PhD, Juan Marcos Gonzalez, PhD, F. Reed Johnson, PhD

Value Health. 2020; 23(11):1438–1443.

Implications of a study appearing in the November 2020 issue of *Value in Health* go beyond health economics and outcomes research. Many nations have struggled with optimal decision making regarding the best balance between social distancing measures and the impact of those measures on the economy. There are polarizing debates at the government level but also at the local community level in all countries. There are very strong preferences one way or another in some groups of society. At the same time, there is a lack of understanding of the preferences of the broader population regarding the trade-offs, and how many people truly prefer one over the other, and how many would be willing to trade off.

The authors set out to quantify the trade-off and to identify groups of people with distinct preferences for public health benefits versus alleviating/avoiding economic hardship. A discrete choice experiment was designed and conducted on a representative sample of the US population to elicit preferences weighing social distancing restrictions against economic impact.

A set of 5953 responders (a representative sample of the US population) completed a survey in May 2020. The survey described COVID-19 risk in terms of overall infection rate (2% to 20%) for the population; the duration of the restrictions on nonessential business (hairdressers, fitness clubs, retail stores) from 0 to 5 months; the economic impact in terms of the percentage of households that would fall below the poverty threshold and the duration of the economic impact, measured in terms of number of years to recovery. Preferences were elicited by asking participants to rank the importance of lifting 6 types of restrictions (eg, schools, restaurants, churches, museums).

Results of the study were presented in terms of ranking of factors in the overall set of responders and showed that nonessential business was thought to be the most important (somewhat surprisingly!), keeping schools open was the second most important, followed by dine-in restaurants; and bars/museums.

Then, a latent-class analysis was used to segment the participants into different distinct categories. Four groups, labeled by the authors (with the percentage of the US sample in the parentheses) as the risk minimizers (36%), the waiters (26%),

the recovery supporters (25%), and the openers (13%) were identified and described. The “risk-minimizers” focused mostly on reducing COVID risk and overall death burden; the second group preferred to wait with opening of nonessential businesses, independent of COVID-risk, but cared about rising poverty levels. Group 3, the “recovery supporters” focused on economic recovery as more important than reducing overall COVID risk. Finally, the last group had a very strong preference for opening. The authors investigated the associations of the socioeconomic characteristics of participants to group membership and both expected and unexpected associations. Having a political affiliation made one more likely to be a risk minimizer, relative to being politically “independent.” Living on a low income means that these people care less about economic recovery; as the authors say, “it would hold little promise for them.”

The authors assessed willingness to accept social distancing measures in the context of overall COVID risk, longer economic downturns, and more families falling below the poverty line, and go on to provide a more granular picture overall. The study's major limitation is that the scenarios were hypothetical and preferences were stated, rather than revealed.

The results of the study may not be easily generalizable; also it seems that in the second wave of the pandemic, some circumstances already changed: people have quarantine fatigue and preferences about COVID restrictions could have changed given that one has to look at a longer time horizon than the 5 months tested in the study. However, the study adds valuable insight and provides a more nuanced picture about the factors that people consider and place value on. Some of these implications will have lessons for decision makers and potentially for business owners as well, not just in the United States but in many other countries. •

FROM THE PATIENTS

Using Patient Preference Information in Medical Device Regulatory Decisions: Benefit-Risk and Beyond

As the use of patient preference information grows in the healthcare industry, ISPOR and the US Food and Drug Administration (FDA) Center for Devices and Radiologic Health cosponsored a [virtual meeting](#) in September on “Using Patient Preference Information in Medical Device Regulatory Decisions: Benefit-Risk and Beyond.” Featuring experts from the FDA, ISPOR, medical device manufacturers, health economics, healthcare, and patient groups, the 4 sessions in the Summit clarified what patient preference information is and presented case studies for the use of patient preference information in decision-making processes, methodologic issues for patient preference information, and future opportunities for the implementation and use of patient preference information beyond the regulatory space.

Background on Patient Preference Information

Brett Hauber, PhD, Senior Economist/Senior Fellow at RTI Health Solutions and Anindita “Annie” Saha, Director, Partnerships to Advance Innovation and Regulatory Science, Center for Devices and Radiologic Health, discussed what patient preference information is and is not, and what the FDA is looking for from manufacturers when they submit patient preference information as part of their application.

Although most of the discussions at the seminar focused on how patient preference information can be used in generating quantitative assessments, “We do not want to forget that qualitative assessments can also have a role in patient preference information and provide valuable information for decision making,” Hauber stated. The “relative nature” of preference is important, because it not only includes the “good” things that are desirable, but the “bad” things that are acceptable. “Both of these are components of preferences that matter,” Hauber said. In looking at preferences, the focus needs to be on the features, both positive and negative, that differ among the alternatives.

According to Saha, patient input can help inform product design, clinical trial development, and also be used to identify specific patient populations that prefer the benefit-risk for specific treatments or to communicate treatment preferences. Additionally, patient input can raise or confirm problems that may exist with specific products and bring to light new considerations to inform FDA’s thinking on current issues.

Above all, submission of patient preference information is voluntary and does not have to be part of every medical device application as it may not be relevant to all device types, Saha said. She continued, “Patient preference information could be useful when usage or decisions by patients or healthcare professionals are preference-sensitive. Some examples of preference-sensitive (decisions) include where there might

be a direct patient interface, where the device could directly affect health-related quality of life, for certain lifesaving high-risk devices, or maybe in an area with a new technology.”

Saha suggested that manufacturers interested in including patient preference information approach the FDA through a presubmission to discuss the regulatory relevance, research question, survey participants, survey design, and analysis approach.

Case Studies Demonstrating Use of Patient Preference Information

Dan Harfe, Vice President, Regulatory, Quality and Strategy, Smith+Nephew (S+N), described a study performed by S+N’s ENT business in which preference testing was used very early on in the regulatory process, when designing a protocol for a pivotal study for a combination product premarket approval. The medical product was an alternative to tympanostomy under general anesthesia for treating young children with otitis media (inflammation of the middle ear). The combination product (device-drug system) enables tympanostomy placement in a doctor’s office using local anesthesia. While avoiding the problems of pediatric surgery under general anesthesia and the stress and worry this gives to parents, the alternative procedure introduced its own challenges. “Toddlers typically do not like you to do things to them,” Harfe noted. And while tympanostomies under general anesthesia have a virtually 100% success rate, the alternative would have a lower rate of success, a common characteristic of pediatric procedures when general anesthesia is not used.

“We do not want to forget that qualitative assessments can also have a role in patient preference information and provide valuable information for decision making.”

The question that arose was whether or not parents would accept a lower rate of success with the novel in-office tympanostomy procedure as compared to the traditional tympanostomy using general anesthesia. To determine an acceptable success rate, S+N conducted qualitative interviews, followed by a preference study, enrolling parents. Completing the preference study and negotiating the acceptability of the data with FDA took longer than initially anticipated. “I suspect that would have gone a lot quicker and smoother if we had engaged with the agency ahead of time,” Harfe said. He noted 4 lessons from the experience. First, make sure to send your study to the right experts at the FDA. Second, treat your preference study like a clinical study from a timeline, budget, and statistical

rigor perspective. Third, work with the right external partners if you do not have the expertise within your own company. And fourth, engage your work with the FDA early in the process. While it may seem like a straightforward decision to gain alignment with FDA ahead of running a preference study, for a start-up with limited financial resources and time, it is not always a simple choice to make.

Christine Poulos, PhD, Senior Economist and Global Head, Health Preference Assessment, RTI Health Solutions, described her experiences using patient preference information to support a premarket approval for PneumRx endobronchial coils, an emphysema product that could provide an alternative to lung volume reduction surgery. The preference study was conducted to support the product's benefit-risk assessment, so it was performed later in the development process. The study used a discrete choice experiment, with the research protocol submitted to the FDA as a formal pre-submission before the survey pretest was completed. There was an in-person meeting to discuss the FDA's comments on the presubmission, with no additional engagement until the study was completed and the results were submitted to the FDA. After that, there was a period of interactive review before the panel meeting.

According to Saha, patient input can help inform product design, clinical trial development, and also be used to identify specific patient populations that prefer the benefit-risk for specific treatments or to communicate treatment preferences.

Patients did not understand the clinical endpoints in the pivotal trial, which made it difficult for them to state a preference. Ultimately, the company was able to develop a patient preference information study based off a secondary patient-reported quality-of-life measure, which generated some noteworthy results. However, the advisory panel had fundamental concerns about the overall efficacy of the coils and ultimately voted to reject the premarket approval on that basis. Two stated lessons were: 1) manufacturers need to strike a balance between the level of engagement with the FDA during the study development period and the time it adds to the study timeline; and 2) there are still no guidelines in the literature or regulatory guidance for how to adapt a patient-reported outcome measure for use in a patient preference information study.

Todd Snell, Senior Vice President, Quality Assurance, Regulatory and Clinical Affairs, NxStage Medical of Fresenius Medical Care North America, reviewed NxStage's experiences using patient preference information to expand the labeled indications for use of their home hemodialysis system. At the time the application was developed, home hemodialysis was underutilized. When the system, NxStage System One, was originally developed, the labeling stated that all treatment "must be observed by a trained and qualified person considered to be competent by the prescribing physician." Snell pointed out that for many patients needing treatment 10 to 15 hours a week, also needing a

competent observer was another burden that most could not meet.

Exploratory discussions with the FDA revealed that the company needed to identify risk tolerance thresholds for experienced home hemodialysis patients who would be willing to perform solo home hemodialysis and also determine if experienced patients would perform it after considering the benefits and risks. The company found a surprisingly high risk tolerance among these patients for things such as death and needle dislodgment. Ultimately, the company was able to get the updated labeling approved, with patient preference information providing a way for NxStage to move its product forward. Snell says that when developing patient preference information studies, manufacturers should know their audience, understand their device's risks, seek feedback prior to the study, and engage early with the FDA to leverage some of the tools the agency has in order to better communicate with patients.

Barry Liden, Vice President, Patient Engagement, Edwards Lifesciences, talked about the study Edwards Lifesciences performed for severe aortic stenosis. Anecdotally, patients voiced concerns about aortic valve replacement, which requires open-heart surgery, expressing a preference for transcatheter valve replacement, which does not require open-heart surgery and which patients considered vastly superior. The Centers for Medicare and Medicaid Services (CMS) and government payers outside the United States were looking only at clinical endpoints, primarily all-cause mortality at 12 months; in this, the 2 procedures were somewhat equivalent.

Edwards set out to design a patient preference information study to inform reimbursement, hoping to bring to the table "qualitative data that could help inform their decision-making process," Liden said. To determine the attributes to study, the company looked at other patient preference studies, sought extra consultation with patients and clinicians, and did a clinical literature review. Instead of a discrete choice experiment, Edwards opted for an adapted swing-weighted study design.

Ultimately, the company found that patients were willing to tolerate a very high amount of risk to receive the benefit. When Edwards took the data to the CMS, while the agency appreciated the information and thought it was very helpful, "they really struggled with how to apply it to a coverage decision," Liden said. The lesson learned, Liden said, was "talk to the people that you are going to be using the data with before you start the study."

Edwards published the data from their preference study and it was picked up in a literature review by Ontario Health, a health technology assessment (HTA) body in Canada, which reviewed this as a part of their overall assessment. Using this patient preference data along with the clinical and economic evidence, Ontario Health made a recommendation to cover this therapy under an expanded indication to low-risk patients.

In the Q&A after the session, Liden said while it was just luck that Edwards' study was picked up by Ontario Health, there are HTAs around the world quite interested in patient preference information, and ISPOR had done an assessment of which HTAs are looking at patient preference evidence and what kind of data

they want to see. “Examples are CADTH in Canada, NICE in the United Kingdom, and Germany’s HTA. Coming to the table with preferential data, quantitative data, is even more robust and helpful to their decision-making process,” Liden said.

Methodologic Issues in Patient Preference Information Studies

David Gebben, PhD, Assistant Professor, Calvin University, and formerly of Center for Devices and Radiologic Health, examined considerations for choosing a method to gather patient preference information. He recommended the document that the Medical Device Innovation Consortium has produced that summarizes some of the qualitative steps to be considered in a survey. Steps include identifying the relevant research question; defining the study results of interest; defining the preference elicitation method and study design; and making sure that the research question is aligned with the study’s objective. The discrete choice experiment (DCE) method “is probably the most familiar, and the one that is probably the most commonly used,” Gebben said, because it allows for the evaluation of multiple attributes at once and can inform endpoint selection prior to clinical trials as well as benefit-risk analysis. Its drawback is that it is “cognitively burdensome” because respondents are evaluating multiple things at once. Alternatively, the threshold technique can be used in the same ways as DCE, but unlike DCE, it only evaluates one attribute at one time. Other methods include: (a) best-worst scaling, which could be used to inform the prioritization of the endpoint selection, especially earlier on in the product life cycle where it is uncertain which endpoints are the priority, and (b) swing weighting, which can be used with rare or hard-to-reach populations. “We have more tools in that toolkit than just the DCE,” Dr Gebben said. “And whatever the analysis that is chosen, we want to be mindful that it should be robust, it should address the research question, and it should be relative to the relevant medical [or] regulatory decision.”

“We have more tools in that toolkit than just the DCE,” Dr Gebben said. “And whatever the analysis that is chosen, we want to be mindful that it should be robust, it should address the research question, and it should be relative to the relevant medical [or] regulatory decision.”

Ryan Fischer, Senior Vice President, Community Engagement, Parent Project Muscular Dystrophy, discussed its experience with using different methodologies and preference research through its BRAVE initiative, the goal of which was to better quantify and understand how patients and caregivers think and feel about emerging therapies and living with Duchenne muscular dystrophy to better communicate to regulators and other stakeholders the preferences of patients and caregivers. “Patients are involved from the start to the finish developing the instruments, the research questions, attributes, and helping to interpret the results,” Fischer said.

Juan Marcos Gonzalez, PhD, Assistant Professor, Department of Population Health Sciences, Duke University School of

Medicine, emphasized that preference data, not preference methods, must be evaluated to determine whether patient preference information is fit-for-purpose. While methods might have some inherent properties, decisions made during study implementation can have far greater impact on the fit of patient preference information. Evaluating fit requires considering at least 3 aspects of a patient preference information study, which he called “the 3 legs of a stool.” Gonzalez said, “We need to consider whether we ask the right questions to patients, whether we are making reasonable assumptions about the answers we get from the patients, and whether the data we collect supports the assumptions we are making about patients’ answers.” For example, instruments should consider both positive and negative framing of the preference elicitation questions. In addition, questions must be incentive-compatible to increase the chance that responses are preference revealing. Some important assumptions about patients’ responses include the form of the measurement error in patient preference instruments, and the type of preference heterogeneity in the data. Finally, support for the assumptions can be obtained within studies through response consistency checks, and across studies through meta-analyses.

In sharing what Janssen and the IMI PREFER public-private partnership have done with data from preference studies, Bennett Levitan, MD, PhD, Senior Director, Benefit-Risk Assessment, Global R&D Epidemiology, Janssen R&D Pharmaceutical Companies of Johnson & Johnson, said that the application of preference study results to clinical data is not always clear or straightforward. He outlined 3 broad classes of approaches to applying preference data: (1) assessments based on the preference study independently (eg, maximum acceptable risk); (2) assessments in which clinical and preference data are depicted together (eg, plots depicting both preference weights and rates); and (3) assessments in which the clinical and preference data are combined into summary metrics (eg, net clinical benefit, choice share). Levitan described a variety of approaches and how they vary in clarity, complexity, incorporation of population heterogeneity, software requirements, complexity of communication, and relevance to different types of decision makers. “In general, I recommend using the simplest approach that will address the research question, but often I end up using a combination of approaches,” he said, adding, “... the real-world applications, taking into account heterogeneity, the variance, uncertainty are not always as straightforward as we would like.”

Implementing Patient Preference Information Beyond the Regulatory Space

First to tackle the implementation, collection, and use of patient preference information beyond the evaluation of product-level benefit-risk in the regulatory space was Dean Bruhn-Ding, Vice President, Regulatory Affairs and Quality Assurance, CVRx, Incorporated. Bruhn-Ding chairs a novel working group for the Medical Device Innovation Consortium, a project that was a first-of-its-kind collaboration, in which 6 industry sponsors collaborated on a patient preference information study with patients, the FDA, and Duke University preference experts to provide valuable heart failure patient preference information for all to use. The Heart Failure Patient Preference Study was developed to inform on a potential heart failure clinical

trial design and provide a regulatory reference for the FDA. “Our challenge as a medical device industry is to use patient preference information studies across the medical device life cycle so that patient perspectives are infused into the entire ecosystem,” he said.

Ravi Jayadevappa, PhD, Research Associate Professor, Perelman School of Medicine, University of Pennsylvania, presented the results of another study, the Preferences for Prostate Cancer Care (PreProCare) tool, which was intended to help patients with prostate cancer assess their preferences for treatment choice in real clinical settings. The preference assessment intervention is a web-based tool that uses choice-based adaptive conjoint analysis. According to Jayadevappa, the intervention group reported higher satisfaction with their care, and higher satisfaction with their decision, but a lower regret across all timepoints, especially at their 12- and 24-month follow-up visits.

Melissa West, Acting Vice President for Research, Discovery, and Innovation, American Society of Nephrology Alliance for Kidney Health, talked about a patient preference initiative that was introduced earlier this year through a partnership with the FDA to develop a survey for a future wearable renal replacement therapy devices. “We are trying to think early about how can we bring the patients into the process, because there is not a wearable hemodialysis machine or peritoneal dialysis machine on the market right now, but we want to bring in this benefit-risk discussion earlier on in the process to ensure that we all really understand what elements of the product and the attributes are most important to them,” she said. Additionally, the group wants to bring patient preference information to payers.

Louis Jacques, MD, Chief Clinical Officer/Senior Vice President, ADVI, said there are still many questions about how to create policy around patient preference information, especially for payers. “Is one going to do a randomized study of every patient preference outcome before one then graduates into some other bucket where it might be used? I mean, that seems impractical,” Jacques says, “Yet we know from our own history that sometimes what seems intuitively appealing turns out, in fact, to be wrong.”

According to Jacques, payers can get frustrated when a pivotal trial misses a primary endpoint, but “then everyone engages in

this post hoc data dredging to say, ‘hey, look, we were better on a subpart of SF-36 that we sort of serendipitously happened to collect.’ Well, congratulations. You now have a hypothesis. Go run a trial with that as your primary prespecified outcome and we might have some more interest in talking to you.”

Manufacturers may want to incorporate discussions about outcomes in the application process for Medicare and other payer coverage in IDE trials. “Medicare loves outcomes data that reflect the beneficiaries’ experience of disease, their experience of priorities, and their response to therapies,” Jacques said.

Conclusion

With nearly 2000 registrants from more than 85 countries, the Virtual ISPOR-FDA Summit 2020 demonstrated a growing interest in the field. Attendees showcased their enthusiasm for patient preference information by actively engaging with thought-provoking questions and discussions. Speakers expressed the importance of incorporating patient perspectives throughout the total product life cycle of medical devices. Thoughtful and well-designed patient preference studies can yield information that can be relevant in not only regulatory decision making, but also in clinical care paradigms and payer considerations. Continued collaborative efforts and future discussions are critical to advance the science and application of patient preference information.

[View the archived webcast here.](#)

About the Author

Christiane Truelove is a healthcare journalist based in Bristol, PA.

FROM THE REGIONS

How Health Technology Assessment Supports Universal Health Coverage in the Asia Pacific

Robert Selby, MBA, Director, Global Networks - Asia Pacific and Latin America, ISPOR, USA

While the COVID-19 pandemic has greatly disrupted health systems in the Asia Pacific region and globally, health technology assessment (HTA) has remained a pillar for healthcare decision making over the long haul. Recently, HTA's role in informing countries' policies around the prioritization and allocation of critically needed resources in hospitals and generating rapid reviews of technologies for emergency use has been essential during the pandemic. But even before the pandemic hit, many countries in the region were already on the long journey toward adopting or strengthening universal health coverage frameworks in their health systems. Throughout that process, HTA has been an indispensable tool for supporting the development of health benefits packages (HBP) within the UHC frameworks, by providing evidence-based recommendations surrounding both the clinical efficacy and the cost-effectiveness, financial, and society-wide implications of interventions. In this way, HTA has helped policy makers make practical reimbursement and coverage decisions that balance the conflicting pressures of providing citizens with broader access to comprehensive care while also maintaining fiscal sustainability for the health system.

COVID-19: Disruptor and Accelerator in the Healthcare Landscape

To better understand how the COVID-19 pandemic has impacted HTA bodies in the Asia Pacific region, the ISPOR HTA Council fielded a survey among its HTA roundtable delegates asking the question, "What are the key challenges and opportunities that have surfaced as a result of COVID-19 from the regional perspective?" Figure 1 shows the specific challenges (orange tiles) and opportunities (blue tiles) raised by the respondents. From the delegates' perspective, the challenges clearly outweigh the opportunities, and a major question was raised: "What is the role of HTA agencies in advancing accurate, evidence-based information

to the public?" According to Dr Li Ying (Grace) Huang, Director of the Division of the Health Technology Assessment, Center for Drug Evaluation, Taiwan, "The importance of fair and transparent decision making and the consideration of patients and public preferences around the availability of high-cost medicines are likely to become increasingly prominent. HTA is well-placed to consider the value proposition from a broader social and health system perspective rather than solely from a patient perspective and has become an essential priority-setting process that adopts the principles of procedural justice and is used to inform policy and access decisions." It seems that even under the current pandemic situation, HTA's role in providing objective and unbiased information remains crucial to ensuring that decisions are taken in a transparent and evidence-based manner.

HTA and UHC: Supporting Patient Access Across the Asia Pacific Region

In Taiwan, continuous reform under the National Health Insurance program has resulted in the expansion of health insurance coverage to over 99% of the

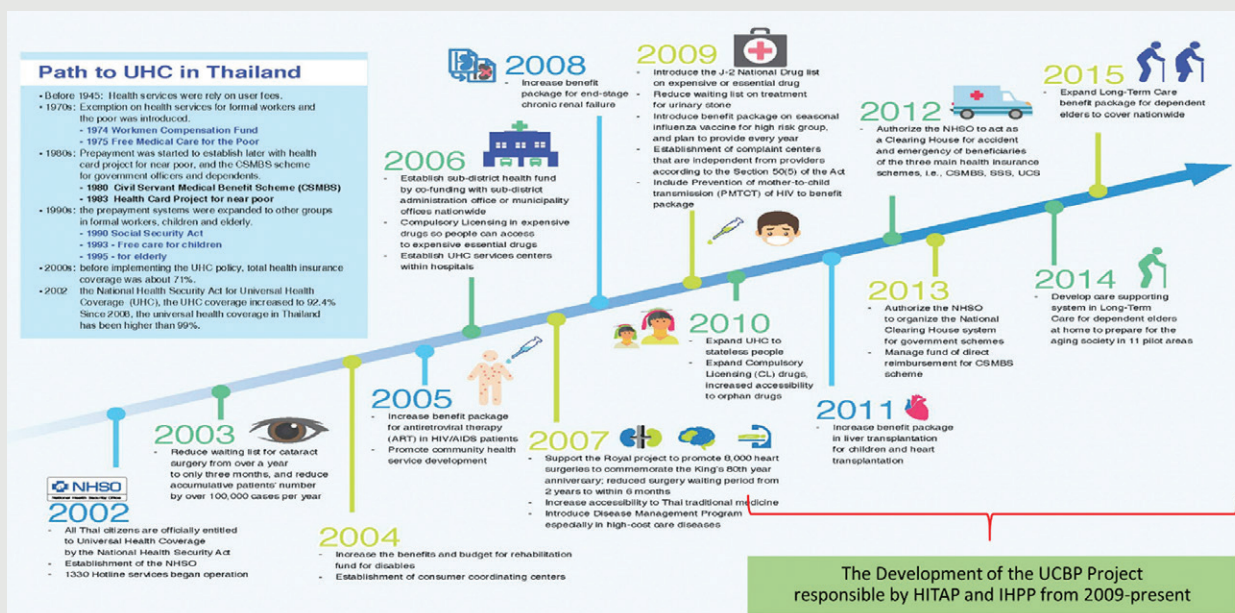
23.4 million population, while keeping premiums and copayments low for citizens. When it comes to the role of HTA in evidence-based policy-making in Taiwan, HTA's stated goal is to support the health authority to maximize the public health benefits. Specifically, the HTA team under the Center for Drug Evaluation primarily assesses the clinical comparative effectiveness and economic evaluation of new drugs and medical devices to support the decision making of the National Health Insurance program. A significant feature of Taiwan's process is the mechanism for consideration of multistakeholder and multidisciplinary perspectives. Taiwan's HTA process follows a well-rounded deliberative framework that covers 4 pillars: (1) budget and financial impact, (2) human health (comparative effectiveness and safety), (3) cost-effectiveness, and (4) medical ethics (unmet medical need). This comprehensive approach allows for broader consideration of the value of health technologies.

In Thailand, there are 3 different insurance schemes covering different segments of the population. Together,

Figure 1. Specific challenges (orange tiles) and opportunities (blue tiles) raised by the respondents

COVID-19: Key Challenges and Opportunities for Health Systems		
Increased international collaboration around procurement of vaccines	Opportunities for disinvestment	Increased use of telehealth and electronic prescribing
Increased demand for rapid reviews with limited information	Deferment of care for chronic conditions	Managing uncertainty in health and economic resources
Supply chain issues	Increased need to strengthen central and provincial storage	Budget and resource allocation
How to fund healthcare given reduced GDP	How to fund healthcare given reduced GDP	What is the role of HTA agencies in advancing accurate, evidence-based information to the public?

Figure 2. Expanding benefits package under the Universal Coverage Scheme in Thailand



Credit: Thailand NHSO. Presented at ISPOR HTA Roundtable Asia Pacific, September 2020

they cover a combined 99% of the population of 66 million. While 2 of the 3 programs include a closed ended annual budget, the benefits package has consistently expanded through the universal health coverage (UHC) framework since 2002 (Figure 2). HTA plays a key role in determining which technologies receive approval and coverage, considering the dimensions of cost-effectiveness, budget impact, and feasibility. Approved pharmaceutical products are included in the National List of Essential Medicines and non-pharmaceutical products are included in the UHC benefits package scheme. The recently updated 2020 HTA guidelines for Thailand have included new sections that provide further clarification on issues such as feasibility studies of the use of health technology, the use of real-world evidence in HTA, and the evaluation of health economic value for health technology in biosimilar products, codependent technologies, health promotion measures, complex health intervention measures, and the measures for rare diseases (Suchonwanich, N. Virtual ISPOR Asia Pacific 2020 Plenary session, Sep 2020).

In South Korea, patient access to therapies is expanding through key programs such as financial-based risk-sharing agreements, which have experienced a marked increase in prevalence (there were 11 risk-sharing agreements in 2016 compared to 35

in 2020). A coverage expansion policy by the National Health Insurance (NHI) program has also led to an increase in the overall coverage rates for interventions, where provisions are made for selective or preliminary coverage of novel therapies with subsequent evidentiary development over a 3- to 5-year timeline. These arrangements are accompanied by tiered rates of coverage ranging from 50%, 20%, and 10%. There also has been an expansion of indications for some procedures, such as magnetic resonance imaging and ultrasonography. The program encompasses 170 items including transcatheter aortic valve implantation and navigation procedures for surgeries. To speed up the assessment process, a parallel review for medical device-related procedures has been instituted where simultaneous review is undertaken by the Ministry of Food and Drug Safety (safety and efficacy), National Evidence-Based Healthcare Collaborating Agency (nHTA, or HTA of medical devices and procedures), and the Health Insurance Review & Assessment Service (reviewing existing comparators) to streamline the approval of technologies. The combination of these new reforms and approaches has made a significant impact on patient access; for example, in vitro diagnostics are now subject to faster uptake with nHTA suspended for 1 to 5 years, where they are managed with preliminary coverage and ongoing real-world evidence assessment.

In India, the Ayushman Bharat UHC scheme of the Government of India has expanded its coverage to more than the initial 40% of the population through its comprehensive primary care centers, along with the Pradhan Mantri Jan Arogya Yojana (PMJAY) health insurance scheme covering secondary and tertiary healthcare centers. The institutionalization of HTA in the country since 2017, aided by capacity building for evidence-based policy making, is envisioned to play a crucial role towards strengthening UHC in India. The cost evidence from the Nationwide Costing Initiative of the HTA body in India has guided the price setting of PMJAY health benefit packages during its revision. Within the Indian context, 3 dimensions to consider when moving towards UHC include equitable access to health services, provision of good quality services to maximum people, and reduction in financial risk.

In mainland China, HTA systematically informs revisions to the essential medicines list, which is the list of therapies covered by the national health insurance program. Established committees regularly evaluate and adjust the essential medicines list every 3 years, prioritizing drugs with clear evidence of effectiveness, safety, and significant cost-effectiveness. In conducting the HTA, the following dimensions are considered: safety, effectiveness considering the available evidence, economy,

innovativeness, appropriateness, and accessibility. The consideration and judgment of value is also becoming broader, with key value dimensions going beyond traditional clinical and economic value to include social value (Figure 3). Multicriteria decision analysis (MCDA) is also employed as a comprehensive value judgment tool to capture preferences and perspectives from a wide range of healthcare stakeholders including patients, physician and pharmacist groups, hospital and medical service providers, healthcare payers, and government. Based upon the review results, there are several potential positive outcomes for recommendation, including acceptance into the reimbursed list of essential medicines; conditional acceptance that may be deemed appropriate for certain subgroups, indications, dosages or routes of administration; or even deployment in pilot implementation. These new avenues for consideration and approval all provide an added measure of versatility and flexibility and expand new pathways for patient access.

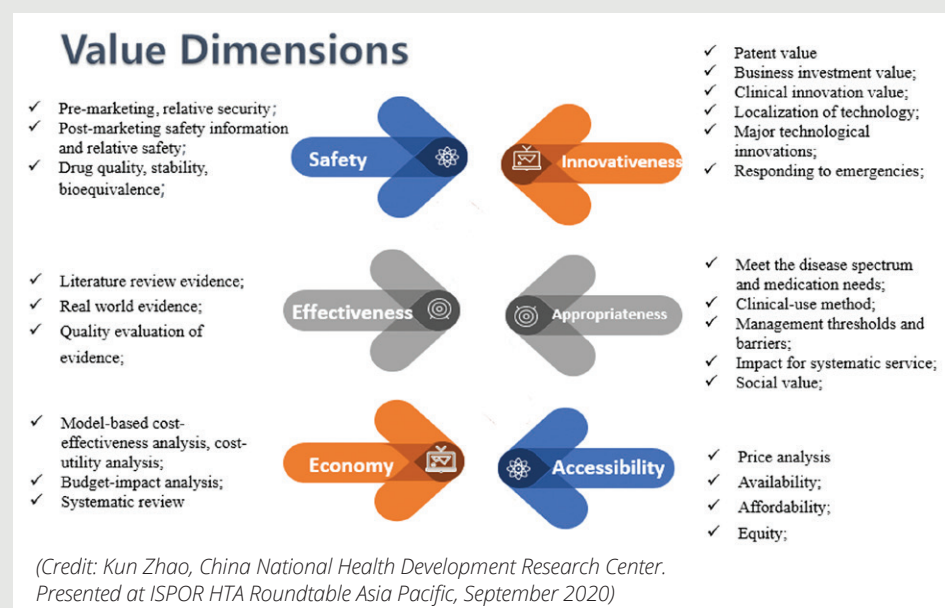
It is clear from these developments that traditional methods of HTA and health

resource priority settings have been severely challenged by the COVID-19 pandemic. Despite these challenges, HTA still remains a critical tool for helping health systems to inform their decision-making processes and the process is becoming more inclusive for stakeholders across the region. It remains to be seen

how HTA will adapt to the post-COVID landscape and what lessons jurisdictions can learn from each other to respond to pressing challenges.

For more information on ISPOR HTA-related initiatives, please visit: <https://www.htacentral.org/>.

Figure 3. Value dimensions in China



ISPOR AWARDS

What Does It Take to Be an Outstanding ISPOR Regional Chapter?

An Interview With the ISPOR 2020 Outstanding Chapter Award Winners: Austria, Mexico, and Mongolia Chapters

The ISPOR Outstanding Chapter Award program recognizes ISPOR regional chapters' outstanding contribution and leadership in advancing ISPOR's mission in global regions: Asia, Latin America, and Europe, Middle East, and Africa. The ISPOR Austria, Mexico, and Mongolia chapters have been recognized for their exemplary achievements in advancing health economics and outcomes research (HEOR) in their regions. The award is based on a thorough review of chapters' compliance with ISPOR governance, input to ISPOR publications, and contribution to ISPOR activities throughout the year as described in their annual reports.

Editor's Note:

Value & Outcomes Spotlight talked to the presidents of ISPOR regional chapters that were recognized with this year's Outstanding Chapter Award and asked them to reflect on the COVID-19 crisis and the postpandemic world in their regions.



ISPOR Austria Chapter

Beate Jahn, PhD
ISPOR Austria
Chapter President

What qualities/aspects of your chapter (activities) are you most proud of? How will you ensure this success will continue next year? What would you hope to improve or develop in your chapter for 2021?

The ISPOR Austria Regional Chapter is very proud and feels extremely honored to receive the Outstanding Chapter Award from ISPOR, the leading global scientific and educational organization for health economics and outcomes research. The aim of the Austrian chapter is to provide a platform for networking and to actively engage different healthcare stakeholders. With our established working group on "Applied Digital Data Transformation and Strategic Patient Empowerment," we connect patient representatives, academia, government, industry, and healthcare professionals.

"We were happy that our rather small chapter led an international exchange about 'Strategic Patient Empowerment and Digital Data' at our ISPOR Forum at ISPOR Europe 2019, sharing Austrian successes and challenges in healthcare practice with the broader ISPOR community and discussing international comparisons to make it a joint learning experience with identified research gaps."
- Chapter President Beate Jahn (UMIT – Tirol)

Our goal for 2021 is to strengthen the chapter by supporting our diverse members in the wake of COVID-19 in making evidence-based, informed healthcare decisions through digital administrative/real-world data analysis, linkage, patient engagement, and health technology assessment developments. Come and join us!

What do you consider are the most important lessons learned from the COVID-19 crisis and how this will affect the future of healthcare? What are some of the health policies that have come out of the COVID-19 pandemic in your country?

The most important lessons learned from the COVID-19 crisis is how to come together in a

crisis regardless of political agenda or personal beliefs.

Austria's Chapter Vice president, Noemi Kiss (ÖGK) acknowledges that one of the most impressive examples was Austria's fast and successful expansion into digital health, including digital prescriptions and doctor's visits. It was a vital step in order to uphold high-quality care, especially for patients with chronic conditions during and after the COVID-19 lockdown.

Efficiency of the new system and processes established under immense time pressure are now being evaluated and adjusted to ensure sustainable healthcare improvement. Due to COVID-19, public health data collection, systematic evidence synthesis, and decision-analytic modeling using sound methods combined with evidence-based risk communication are more relevant than ever. We are grateful to chapter members and colleagues who worked tirelessly to produce high-quality, timely, and relevant information to support healthcare decision making and initiate new HEOR related COVID-19 research projects.

What are your thoughts on the post-pandemic world, and what do you think will be the role of HEOR?

The role of HEOR is expanding further into political thinking and decision making on all levels of government, into clinical practice and public discussion. We are proud to be part of ISPOR, a society in which members push the boundaries of HEOR research to improve healthcare for all.

When we discussed with Niki Popper (DEXHELPP, TU Vienna), our former founding Chapter President, who is a modelling and simulation expert for the Austrian Ministry of Social Affairs, and member of the Consumer Protection's COVID-19 Task Force, he mentioned that "HEOR topics, including efficient utilization of scarce resources, and stakeholder-relevant preferences and outcome measures, as well as principles of equity are a driving force for decision making. In the postepidemic world, digitalization, telemedicine, and artificial intelligence will be applied to complex health and economic data to support a healthcare system that is sustainable and responsive at the same time."



ISPOR Mexico Chapter

**Cesar Alberto Cruz Santiago, MSc,
PhD, MD**

ISPOR Mexico Chapter President

What qualities/aspects of your chapter (activities) are you most proud of? How will you ensure this success will continue next year? What would you hope to improve or develop in your chapter for 2021?

Every month, the ISPOR Mexico chapter prepares sessions to keep members updated on issues of health economics, our healthcare system, or relevant aspects on a day-to-day basis, such as the pandemic and our environment.

One of the aspects that we are proud of as a chapter is that the number of attendees to these events remains constant, even now with the pandemic. Even with remote interactions, people are still interested in staying updated with the chapter. We always strive for these sessions to be of the highest quality, with highly relevant national and international speakers.

Another of the activities with which we are very proud is that we have worked together with the government and industry on a project led by the ISPOR Mexico chapter to establish quality indicators in Mexico and thus be able to carry out economic evaluations (cost-utility analysis) with information from our country. This activity is unprecedented and will surely generate tools that allow the generation of more economic evidence in our country for the best decision making.

Another important development is that the ISPOR Mexico Student chapter is now a reality. After many attempts, its inauguration was finally possible. From the student chapter, we will promote to the new generations the importance of HEOR.

We will work hard to maintain the same interest towards the chapter, generating work sessions in which industry, academia, and government participate in such a way that the members of the chapter continue to be engaged. In so doing, we hope to attract new members, including more students.

What do you consider are the most important lessons learned from the COVID-19 crisis and how this will affect the future of healthcare? What are some of the health policies that have come out of the COVID-19 pandemic in your country?

Although the pandemic has been something that nobody expected, we have learned to work with it. In the case of the chapter, what we have done is continue working to generate virtual meetings to keep people updated. Undoubtedly, this has been a different experience, but it has also helped us because we have been able to have sessions with international speakers through these platforms that allow us to work from home.

The world will not be the same after COVID-19 and the health systems have to adapt to different conditions. The greatest challenge is to continue giving the best attention to patients with COVID and not stop caring for patients with other diseases, such as cancer and cardiovascular and metabolic illnesses.

What are your thoughts on the postpandemic world, and what do you think will be the role of HEOR?

The postpandemic world has a lot to learn. Normal conditions will not be the same as those experienced in March 2020—economic conditions, political conditions, and health conditions are going to be different; resources and budgets will be scarce. In this stage, we will have to make the best possible decisions and we need the best help available.

HEOR will undoubtedly continue to be a tool to improve decision making. HEOR will continue to guide and inform evidence generation that allows us to see the clinical and economic benefits of interventions, especially now in a context where the health system has been affected by the pandemic.



ISPOR Mongolia Chapter

**Ganbat Byambaa, MD, MPH,
MHSM, PhD**
ISPOR Mongolia Chapter President

What qualities/aspects of your chapter (activities) are you most proud of?

Our small but passionate team consisted mostly of academics and policy makers, as well dedicated ad hoc members. Since 2011, almost a decade has passed and I am proud that Mongolia is taking strong and solid steps towards developing and utilizing evidence-based science and promoting and implementing healthcare reforms. Looking back, I am honored that we were involved in numerous research projects and organized even more training and workshops to distribute knowledge and information about health economics, and contribute to building and maintaining communication between different stakeholders, including the public and private institutions. We were also successful in promoting the ISPOR Mongolia Chapter and were able to learn from our international colleagues. In addition, we successfully produced training materials, educational books and an HTA guideline. These documents are essential to the creation of appropriate conversation and guidance for our decision makers and educators.

How will you ensure this success will continue next year?

Next year, we plan to organize our regular trainings and meetings with healthcare stakeholders, researchers, academics, assessors and regulators; payers and policy makers; the life sciences industry; healthcare providers; decision makers and patient engagement organizations. In particular, I would like to emphasize the importance of learning from evidence-based experiences and sharing good practices. Building capacity is an important step towards ensuring the success in future, therefore I would like to recruit more members from various disciplines and increase the representatives of the Society among the relevant stakeholders. Moreover, I plan to support and provide guidance for projects and research works, as well as share our experience with ISPOR Chapters in different countries.

What would you hope to improve or develop in your chapter for 2021?

First and foremost, the ISPOR Mongolia Chapter will hopefully remain active and dedicate to slowly shift towards beyond pharmacoeconomics to consider medical devices, diagnostics, procedures, and other health interventions. I also emphasize that key goals of the ISPOR Mongolia Chapter will be research and scientific excellence and hopefully we will continue to contribute successfully to improving decision making for health, including adopting and implementing good practices in Mongolia. Concurrently, the ISPOR Mongolia Chapter will continue to promote learning, sharing good practices, and building capacity, which are currently essential to our work. Of particular interest is our further work with regards to health technology assessment and efficiency and effectiveness of interventional strategies for COVID-19 response.

What do you consider are the most important lessons learned from the COVID-19 crisis, and how this will affect the future of healthcare? What are some of the health policies that have come out of the COVID-19 pandemic in your country?

Earlier in the year, multisource surveillance did not detect any COVID-19 infections in our communities. As of June 23, 2020, 215 COVID-19 imported cases from repatriated people have been confirmed and isolated in COVID-19 designated hospitals. A majority of these detected cases were recovered (n=158, 73.5%). Currently, there is no high volume of COVID-19 patients admitted to the healthcare system; however, preparing to balance between routine essential services and COVID-19–designated health services in the case of communal outbreak of COVID-19 is of high priority.

Mongolia officially declared a state of high-alert preparedness in February 2020, with a complete lockdown closing all schools, kindergartens, and educational institutions starting from January 27, 2020 and restricting all travel to and from countries with active cases of COVID-19. Implementation of nonpharmaceutical interventions bought the country a precious time window to prepare its health system. The government action based on multisectoral collaboration under leadership of the national emergency commission was undertaken very early, including sweeping public health measures to protect its citizens, and has greatly assisted in minimizing the spread of COVID-19.

What are your thoughts on the postpandemic world, and what do you think will be the role of HEOR?

The world is experiencing the worst crisis in recent history. Being far more than a health crisis, the COVID-19 pandemic is affecting all aspects of societies and their economies, exposing prevailing structural fragilities, and deepening pre-existing inequalities in the countries. Social distancing, school closures, online teaching, work from home, wearing face masks, and hand washing to protect individual safety, and enforced restriction measures for social security are all new challenges and create a “new normal” in our lives.

Universal health coverage and leaving no one behind policies will become important more than ever and require more strategic action from the countries’ governments. Innovation, knowledge sharing, and new ways of thinking will be the most effective way to build capacity and produce best evidence and practice in HEOR areas. Socioeconomic impact analysis, effectiveness and efficiency of clinical management, infection prevention and control measures, and improving health system preparedness and response mechanisms should be important priorities for HEOR. •

Virtual ISPOR 2021 • May 17-20



HEOR: Evolving for Tomorrow's Challenges

2020 has forced many professions, research fields, and industries to an inflection point, requiring verification of direction and opportunities to chart a new roadmap for development. Healthcare systems' resilience and sustainability is being tested to its maximum, challenging prepandemic priorities under unprecedented resource constraints. This has highlighted opportunities and challenges in HEOR methods, practices, and application including our ability to respond effectively.

Join us at Virtual ISPOR 2021 to address the challenging questions that surround HEOR in the time of a global pandemic.


The robust 4-day program includes:

- 4-day live conference schedule tailored to a global audience
- Three plenary sessions
- HEOR expert speakers
- Spotlight sessions which highlight timely topics in HEOR and promote innovative areas of interest to the HEOR community
- Breakout sessions with issue panels and workshops
- Educational symposia
- Virtual poster presentations
- Networking opportunities including live group discussions, social hours, and small group and 1-on-1 chats – your best opportunity to interact with your peers in the HEOR community
- Exhibits and more

*Bonus – New on demand-only content will be available leading up to the live conference!

Abstract Submissions for Research Proposals Close January 13.

 Learn more at www.ispor.org/ISPOR2021

 Join the conversation on Twitter [#ISPORAnnual](https://twitter.com/ISPORAnnual)

Virtual ISPOR Short Courses



Expand Your HEOR Knowledge with ISPOR Short Courses

ISPOR's expert short course faculty present hand-picked virtual courses that provide a solid foundation in essential methodologies and emerging issues. Short Courses each offer corresponding electronic course books. Please note: Short Courses are not recorded, therefore attendance of the live-broadcast is critical.

Introduction to Health Economics Outcomes Research

12-15 January 2021 | 8-Hour | 4-Day Short Course

Designed to teach clinicians and new researchers how to incorporate health economics into study design and data analysis, this course will offer participants a first review of the basic principles and concepts of health economic evaluations, and discuss how to collect and calculate the costs of different alternatives, determine the economic impact of clinical outcomes, including how to identify, track, and assign costs to different types of healthcare resources.

Instructor: Lorne Basskin, PharmD, Charleston University, Charleston, West Virginia, USA.

Introduction To The Design & Analysis of Observational Studies of Treatment Effects Using Retrospective Data Sources

27-28 January 2021 | 4-Hour | 2-Day Short Course

This course will provide an overview of the structures of commonly encountered retrospective data sources with a focus on large administrative data, as well as highlight design and measurement issues investigators face when developing a protocol using retrospective observational data. Approaches to measure and control for patient mix, including patient comorbidity and the use of restriction and stratification, will be presented. Linear multivariable regression, logistic regression, and propensity scoring analytic techniques will be presented and include examples using SAS code that can later be used by participants.

Instructors: Bradley Martin, PharmD, PhD, RPh, University of Arkansas for Medical Sciences, Little Rock, AR, USA; Linus Jönsson, PhD, MD, MSc, Medical Affairs & Clinical Development Centres, H. Lundbeck A/S, Valby, Denmark.

 **Learn more and register for ISPOR Short Courses:**
www.ispor.org/shortcourses

Virtual ISPOR Europe 2020



Thank You Virtual ISPOR Europe 2020 Sponsors and Key Supporters

Newsletter Sponsors



Symposia




Key Supporters



All on demand and live sessions from Virtual ISPOR Europe 2020 are available as recordings. Access to session recordings is available to registered attendees through December 31 [here](#). Slide presentations will be available (subject to speaker approval) at the [ISPOR Presentations Database](#) and on the Virtual ISPOR Europe 2020 [program](#) page beginning January 6, 2021.

Challenges in Precision Medicine:

Aiming to Align Data, Value, and Costs



Precision medicine—also referred to as personalized, stratified, individualized medicine—delivers targeted treatments to specific groups of patients based on individual characteristics. With precision medicine, targeting the right patient with the right drug at the right dose at the right time can potentially improve patient outcomes and decrease healthcare costs.

Since 2014, these drugs have represented at least 20% of all FDA approvals each year. Examples of 2019 precision medicine approvals included Mayzent (siponimod) for the treatment of relapsing forms of multiple sclerosis, Balversa (erdafitinib) for the treatment of locally advanced or metastatic urothelial carcinoma, and Rozlytrek (entrectinib) for the treatment of metastatic non-small cell lung cancer.

Ensuring access to these products presents a challenge as payers struggle to capture long-term treatment benefits. This is especially problematic in the United States where roughly 20% of patients switch healthcare insurance each year.¹

ISPOR's Precision Medicine and Advanced Therapies Special Interest Group (SIG) has provided critical guidance on issues surrounding approval, payment, utilization, and evidence development related to the use of precision medicine. This group released its report on value frameworks for precision medicine in the May 2020 issue of Value in Health, highlighting the need to understand value drivers, challenges, and opportunities from both patient-level and system-level perspectives to ensure ongoing access to precision medicine products.²

Expanding on the SIG's recent report, patient and payer representatives shared their views on recent trends in precision medicine and the ongoing challenge to ensure access. Chris Sotirelis, PhD, provided a patient perspective, while Josh Akers, PharmD, BCACP, CPHQ, and Flemming Sonne shared their thoughts from a payer perspective. These contributors highlight the ongoing concerns and objectives that different stakeholder groups face in their ongoing mission to expand access to precision medicine for patients who can best benefit. These payers represent and extrapolate on how precision medicine has evolved recently and how their organizations are addressing these changes.

Patient Voice Helping to Define Value and Stimulate Orphan Drug Development

For decades, Chris Sotirelis, PhD, previously Vice President of the United Kingdom national thalassaemia patient association, has acted as both a patient advocate and an “expert patient” for rare genetic conditions for a variety of organizations, including the European Medicines Agency. As a patient with β -thalassemia major, an inherited blood disorder in which the body cannot make hemoglobin normally, Sotirelis brings important insight and experience into how patient perspectives may be incorporated into these precision medicine value conversations.

He noted that 20 years ago, there was little patient engagement during coverage and reimbursement conversations. He felt system-level stakeholders expected patients to hold the same goals—that patients merely wanted a wider choice of treatment options and more products to be funded, and therefore their direct opinions were not sought. Instead only clinicians were used to convey what they considered to be patient opinions. “In part, this was driven by the clinicians as well, in that they wanted to have more treatment options,” recalled Sotirelis.

Sotirelis has seen an increase in patient involvement over the past 15 years with expanded support for orphan drug development. Orphan drug legislation, both in the United States and in Europe, has created true incentives for orphan

drug development. Patients are now commonly involved in value discussions, being asked their preferences, while also being invited to share their perspective about what constitutes value. These conversations have become increasingly important as public health system budgets buckle under the financial weight of increasingly expensive drugs.

Patient input in these value discussions is critical because he views value as “where a particular product stands on areas that are directly relevant to patients.” He believes that patient preferences should be incorporated into assessment of benefits and risk.

“I think by having an honest, open, and transparent discussion that includes patient perspectives, you can see the uncertainty and the risk in a different way.”

In Sotirelis' view, every step of the clinical development pathway should involve the patient's perspective of uncertainty. This is especially critical in rare diseases where there is limited understanding of the condition and a lot of variability in the disease due to the heterogeneous nature of these conditions. Particularly in the case of advanced therapy medicinal products, this is compounded by the variability in the product manufacturing process, which has a definite impact on efficacy and clinical outcomes. This is vital for payers to realize when they are trying to assess reimbursement and could potentially become a powerful tool in price negotiation. He argued that development of these precision medicines requires an understanding of the medical needs of that condition and the medical needs of subgroups within the condition. Preferences of patients with chronic diseases, such as β -thalassemia, where through clinical advancement and innovation, over the years, patients are able to have a near-normal lifespan, differ significantly from those with life-threatening pediatric diseases, such as Duchenne Muscular Dystrophy or Spinal Muscular Atrophy. “This kind of variation between the two extremes has to be reflected because it impacts uncertainty.”

Sotirelis argued for greater involvement and true embedding of patients in all decision-making bodies along the entire clinical development pathway for these therapies. “I think by having an honest, open, and transparent discussion that includes patient perspectives, you can see the uncertainty and the risk in a different way.”

Collaboration is the Key to Easing Disease Burden

Sotirelis encourages more interaction between researchers and patient groups. He noted that until recently researchers have not had many opportunities to connect with patients and understand their viewpoints so that patient perspectives may be incorporated into the development process.

He highlighted his involvement with the Mechanism of Coordinated Access (MOCA), a group of payers from different European member states that work with sponsors and

companies during the clinical trial process, discussing the kinds of evidence that may be required to meet payer needs. This process minimizes the likelihood of delays during the contracting process.

He also spoke of his participation with RD-Connect (rd-connect.edu), a European collaboration of scientists, researchers, bioinformatics experts, patients, and public health experts aimed at creating a platform for developing genomic tools and for funding therapies to treat undiagnosed rare diseases.

"I think these collaborations have been very beneficial because it opens up researchers' eyes to what it means to have a specific condition, how your life is affected by that, and what are the points where researchers and patients can interact in trying to fix certain things to ameliorate this burden of disease."

Establishing Accurate Expectations

Representatives from 2 different payer types contributed to this conversation. One, a US payer, where patient engagement is comparatively brief given the high frequency with which US patients change health plans, and the other, a European payer that covers patients throughout their lifetime.

Josh Akers, PharmD, Manager of Pharmacy Clinical Programs, Premera Blue Cross in Seattle, Washington, USA, shared his views from a US-payer perspective. Premera is the largest health plan in the Pacific Northwest, covering more than 2 million patients. It has also been a thought leader among US payers in adopting value-based approaches to its contracting processes.

"I think there's a lot of interest in being very clear in our predictions about expected costs, patient experience, and outcomes."

Akers began his thoughts by emphasizing that his organization wants to ensure that their members have access to new precision medicines. "We want to do the right thing," said Akers. "We don't want to restrict access."

He noted that Premera's insured groups are playing a larger role in expanding access for new precision medicine products. "We have customers asking about very specific products," he said. "They want to know if the client's insured group includes anybody who is on some of these new gene therapies. They want to know what they should expect and what will the impact be when this therapy comes out."

Premera and its clients must predict how these new precision medicine therapies may impact their budgets given how these budgetary changes may affect premiums, deductibles, and benefit plans, especially with self-funded groups.

To better predict the budgetary effects of precision medicine drugs, Akers stated that payers need to better understand who

the potential patient population is and how that population is represented within their membership. And they need to understand both long-term and short-term treatment effects in that population.

Akers revealed that payers may have limited understanding of the rare diseases targeted by many of the new precision medicine therapies due to lack of comparative treatment data, availability of treatment guidelines, etc. "When we're looking at our entire membership, we need to know how does demand for these therapies align with our membership?" These products could have a tremendous impact on small insured pools or a relatively small impact on large insured groups.

Manufacturers' prevalence calculators can be immensely helpful, Akers noted, especially when predicting the budgetary impact of new therapies for large insured groups. However, smaller insurance pools, where treatment for 1 or 2 members could total hundreds of thousands, even millions, of dollars, has a huge budget impact. Akers said, "How do these small groups pay for that?"

Treatment Benefit Complicated by Client Turnover

Premera and their clients also want to clarify treatment expectations: What constitutes "benefit" with precision medicine? Is a new therapy truly meeting an unmet therapeutic need? And over what timeframe? "Is the precision medicine therapy going to reduce their cost over the next 2 years? Over the next 4 years? Six years? If this is a true curative therapy or near-curative type of therapy, what should Premera's expectations be?" asked Akers.

"I think there's a lot of interest in being very clear in our predictions about expected costs, patient experience, and outcomes."

For US payers, the question of treatment benefit is complicated by a pattern of frequent turnover in insurance membership rolls. "You may need to look out 2 years, 4 years, 5 years to really see a benefit. That's where the real return is." But as Akers emphasized, members may have long left Premera by year 5, having switched jobs or moved. In this case, will contracts between Premera and its insured groups cover these treatment benefits?

Establishing Value and Minding the Gaps

According to Akers, Premera recognizes that there are many ways to consider value—understanding the unmet clinical need, including the history of disease, the disease burden placed on individuals, and current treatment options. He noted that ICER reports hold influence over how Premera looks at the value of therapies as they come onto the market. He continues, "We want to include other reviews that may be available. Beyond our own analysis, can ICER and other independent reviews help us establish the value of these therapies, and what kind of fair market pricing should we expect?"

Akers recognizes that manufacturers may differ with ICER's conclusions. However, he emphasized that Premera welcomes manufacturers' arguments regarding ICER's analyses. "We are definitely open to listen. We want to hear the argument."

Gaps in value assessment continue to concern Akers. He noted that nonmedical, humanistic benefits may not be fully incorporated into the value determination of precision medicines. Akers added, “What we don’t see is real-world data on the impact on quality of life. Do patients have more productive workdays? Better quality of life?”

Akers emphasized the importance of patient perspective in evaluating new treatments. Premera highlights its work with patient advocacy groups. “We want to take patient feedback into consideration. We want to hear their perspective,” he stated. While these groups often voice an eagerness to gain access to precision medicine therapies, Akers notes that these patient groups sometimes reveal patients’ hesitancy regarding new products, especially when there may be well-established, safe treatment alternatives. Alternatively, treatments filling a significant unmet need, especially in pediatric conditions where there may not be a treatment alternative that may change the trajectory of someone’s life, are usually a top priority to patient advocacy groups.

Limiting Risk, Increasing Access

Flemming Sonne, CEO, Amgros, Copenhagen, Denmark, expanded on Akers’ system-level perspectives, providing the views of a payer with longer-term patient engagement. While the Danish Medicines Council approves new medicines and determines their added clinical value, Amgros negotiates pricing contracts for all prescription drugs within Denmark.

In his work to make precision medicines accessible and affordable, Sonne discussed Amgros’ work with innovative pricing models. Sonne spoke to the challenge of ensuring access to these products given the limited data on long-term efficacy. “We would like to see the effect of the product before actually accepting to use it fully.”

“Under this kind of arrangement we get an exit door in the contract if the patient’s treatment doesn’t work.”

He emphasized the need for risk-sharing arrangements to overcome the financial uncertainty of a drug’s first few years on the market, stating, “We have to find a way where we will only accept a limited amount of risk with the new product.”

During a products’ initial 2 years on the market when data are sparse, Sonne proposed that manufacturers, or even hedge funds, could assume some of this initial risk by accepting a discounted price until a clearer picture of a product’s long-term efficacy comes into view.

“I think in this case we may go into the negotiation suggesting paying a fifth of the contract in the beginning (ie, only a part of the contract). Then we will follow the quality of patient outcomes.” Sonne noted that this discount would be critical,

especially given the significant costs of administration for these contracts associated with increased data collection.

“Under this kind of arrangement,” Sonne said, “we get an exit door in the contract if the patient’s treatment doesn’t work.”

Amgros has also employed the Netflix model in contracts for these newer therapies, paying a monthly fee for a specific number of patients. He emphasized the uncertainty surrounding which party may benefit most from this model, noting “The manufacturer could be the winner or we could be the winner because we actually don’t know how many patients will be in the treatment.”

Premera is also examining methods to possibly share risk. “I think we have to look at multiple methods. Are there opportunities for outcomes-based rebates or other opportunities for value-based contracts?” said Akers.

One possible approach Akers suggested may be a warranty agreement, such as those used by some providers for total joint replacements. He suggests that with precision medicine drugs, a single treatment providing curative, near curative, or long-term solutions that could help vastly improve someone for the rest of their life, a warranty agreement or other guarantee could be an option.

Data: To Wait or Not to Wait

Insufficient data complicate negotiations over these alternative pricing models for precision medicine drugs. Data used for regulatory approval differs greatly from data needed for access and reimbursement. “We don’t have the evidence or the real-world data in a way to follow (treatment effects),” said Sonne. “But we try to find some models and we work with it.”

Sonne emphasized the complicated task of accessing data. “We know that the data are there. But the way they have set it up at the moment doesn’t work, so we can’t get the data out of the system.”

For high-priced treatments, the lack of efficacy data can limit early access. “The medicine council are quite cool at the moment if you don’t have the data (for a drug with) a very high price with 40 or 50 patients treated. They wait.”

He highlighted the case of orphan drug, Spinraza nusinersen. “As an orphan drug, we don’t have the data. That’s why we haven’t accepted full use of Spinraza until now.”

But Sonne also reflected on the potential ramifications of limiting early access as they await better efficacy data. “Waiting for better efficacy data will cost the lives of some of patients. But on the other hand, it could be that we save some lives.”

The Key to a Long-Term Future Is Short-Term Data

Both Sonne and Akers spoke to what they would like to see from manufacturers. And both voiced the same desire: more data early in process.

“We need access to important data to make accurate calculations based on the price agreements,” said Sonne.

"However, we know that several good initiatives have already been taken to make this possible within the near future."

Akers continued. "We want the data to show the clear markers on how this improves outcomes. What are the real-world outcomes—emergency room visits, inpatient admissions, morbidity/mortality—that are going to improve? We need to know what we can monitor to make sure these are the highest value therapies within these disease states."

"Waiting for better efficacy data will cost the lives of some of patients. But on the other hand, it could be that we save some lives."

Akers reiterated this call for timely data on outcomes and timeframes. "We need to know as early in the development of a drug as possible what outcomes we can expect." He continued, saying, "When we're looking down the road, how do we make sure that patients are getting those benefits within these contracts? What are the checkpoints? Can we pull that data to be able to look at it?"

However, Akers noted the challenge faced by manufacturers in producing these data, especially for precision medicine drugs. "This is one of the toughest things for a lot of the manufacturers and researchers in general. It takes a long time to get these data, and they may not have as much long-term outcome data yet in the process of making these therapies available for patients."

To help their organizations prepare for these new therapies, both Amgen and Premiera invest resources in horizon scanning and in monitoring the drug pipeline. "It's really trying to monitor what's coming down the line and what adjustments are we going to need to make with the precision therapy?" said Akers. In Denmark, Sonne noted that his organization employs horizon scanning to help estimate future year budgets.

Akers notes that monitoring the pipeline for precision therapy products requires additional resources because these therapies are "so specific and have a very unique impact on the niche populations that they're designed for."

Looking at the Partnership of Payers and Manufacturers

Akers welcomes manufacturers bringing their creative ideas about pricing and contracts for these new therapies, such as offsetting risk, as well as how to address members switching insurance plans. For example, how can payers help ensure that patients continue to receive the benefit of a therapy, even when they're switching plans?

Sonne echoed Akers' openness to input from manufacturers during this period of expanded use of precision medicine. "We need a lot of good ideas from the industry. We listen to them. We see them as a partner for us."

References

1. Cunningham PJ, Kohn L. Health. Plan switching: choice or circumstance? *Health Aff (Millwood)*. 2000 May-Jun;19(3):158-164. doi: 10.1377/hlthaff.19.3.158. PMID: 10812794.
2. Being precise about precision medicine: What should value frameworks incorporate to address precision medicine? A report of the personalized precision medicine special interest group. *Value Health*. 2020 May;23(5):529-539.

About the Author

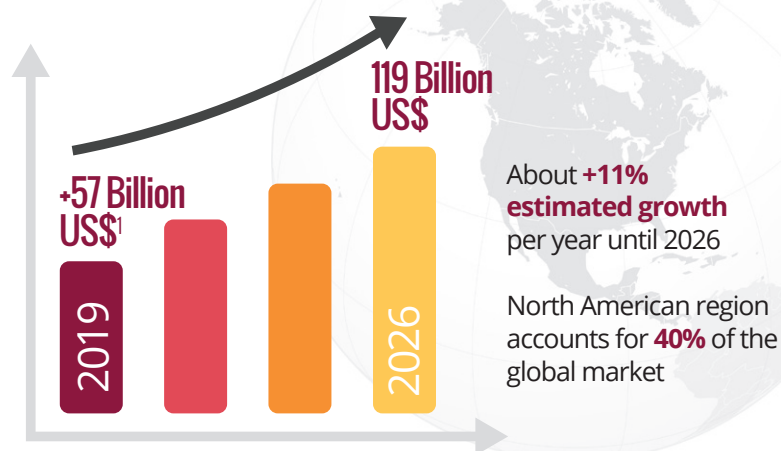
Michele Cleary is a HEOR writer in Minneapolis, MN.

By the Numbers: Global Perspectives on Precision Medicine

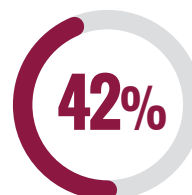
Section Editor: The ISPOR Student Network

Size of the Personalized Medicines Market and Estimated Growth (2026)

Precision Medicine Market Size



Investment Focus in Personalized Medicine³



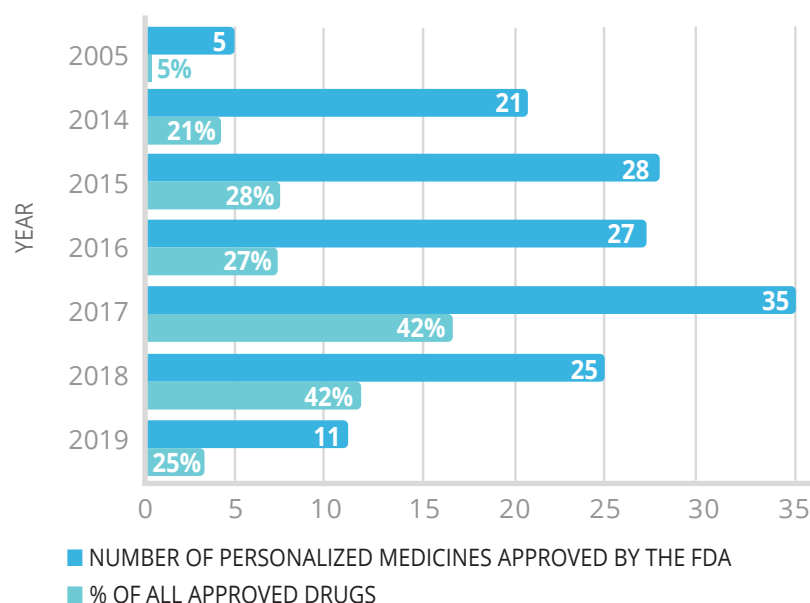
of **all drugs** in development are personalized medicines



of **oncology drugs** in development are personalized medicines

Share of Personalized Medicines in Approved Molecules Keeps Growing

In 2005, only 1 in 10 approvals were precision medicines, whereas today we have 1 in 4.²



4 Main Applications for Personalized Medicine¹



Oncology
Immunology
Central Nervous System (CNS)
Respiratory

References provided online

Contributors: Contributors: Vasco Pontinha, Virginia Commonwealth University, Richmond, VA, USA; Ana Gonçalves, Charité – Universitätsmedizin, Berlin, Germany; Jacinda Tran, University of Washington, Seattle, WA, USA; Shrey Gohil, University of Houston, Houston, TX, USA. **Acknowledgment:** We would like to thank Zeba Khan, RPh, PhD, for her review and helpful comments.

Time for Change? Has the Time Come for the Pharmaceutical Industry to Accept Modest Prices?

Sarah Garner, Honorary Professor, Division of Population Health, Health Services Research & Primary Care, Manchester University, Manchester, United Kingdom; Jens Grüeger, University of Washington, Seattle, WA, USA; Michael Schroter, VIOPAS, Zürich, Switzerland; Kate Dion; 3D Communications, Dollar, United Kingdom

Panelists from the ISPOR Europe 2019 Copenhagen issue panel, “Time for change? Is it time for industry to accept lower prices?” held a virtual meeting this summer to discuss their views on how the pharmaceutical industry should approach pricing in the pandemic.

Kate Dion, former journalist, healthcare thinker, and Value Communications Lead at 3D Communications, has been observing the broader pricing debate for more than a decade. Last year, she convened an Issues Panel entitled, “Time for change? Is it time for industry to accept lower prices?” at the ISPOR Europe 2019 Conference in Copenhagen. This summer, she followed up with panel members Sarah Garner, Michael Schröter, and Jens Grüeger in a virtual meeting to discuss their views on how the pharmaceutical industry should approach pricing in the pandemic. The conversation was an exploratory discussion and did not focus on the pricing approaches of any one company.

The statistics are devastating: as of November 20, 2020, COVID-19 had killed more than 1.36 million people, sickened nearly 57 million¹, and has been forecast to cost the global economy as much as \$28 trillion in lost output over the next 5 years². As the world waits impatiently for therapies and vaccines against this deadly virus, one thing is clear; now is the chance for the pharmaceutical industry to show that its pricing strategies will support, not prevent, rapid global procurement of life- and economy-saving medicines

Gilead Sciences was the first drug maker to develop and price a medicine for COVID-19. Their drug remdesivir, which has been shown to reduce the recovery time of seriously ill patients, will cost governments of developed countries \$2340 for a 5-day treatment course for one patient. Private insurance companies in the United States will pay \$3120. Gilead Chief Executive Dan O'Day, who has pledged to make the drug “affordable,”³ believes these prices are “well below value.”

“Taking the example of the United States, earlier hospital discharge would result in hospital savings of approximately \$12,000 per patient. Even just considering these immediate savings to the healthcare system alone, we can see the potential value that remdesivir provides. This is before we factor in the direct benefit to those patients who may have a shorter stay in the hospital,” O'Day wrote in an open letter that was published on June 29, 2020 and set out the US company's pricing rationale.

Drug makers Johnson & Johnson⁵ and AstraZeneca⁶ have both said they will forgo profits on any medicines they successfully develop for the coronavirus in order to ensure fast and equitable access, while GlaxoSmithKline⁷ and Pfizer⁸ are backing efforts to make products they develop readily available.

Swift Access

“If COVID-19 has shown us anything, it's that we need novel medicines that won't blow the budget and we need them now,” said Michael Schröter, Founding Partner of Swiss-based VIOPAS, a firm that invests only in healthcare companies that develop innovative and cost-saving health technologies.

The answer for drug makers developing COVID-19 medicines may be to adopt a “value-minus” pricing approach, according to Jens Grüeger, Affiliate Professor, University of Washington. “Exceptional times call for exceptional measures. The tremendous benefits that safe and effective coronavirus medicines would bring to patients, healthcare systems, and indeed economies, would result in them quickly becoming unaffordable if the traditional value-based pricing approach were followed,” Grüeger said.

“It is not feasible to ask healthcare systems to pay prices that would fully reflect the improved mortality, morbidity, and quality of life as well as the economic and social benefits linked to a reduction in social distancing and lockdowns that would come from a medicine. Not to mention the savings that could be realized for healthcare systems through

the avoidance of additional infections and lower hospitalization rates and stays,” he said.

Instead, Grüeger believes that when companies are pricing coronavirus medicines, they should consider only the savings that would be generated within the healthcare system so that the budget impact would remain neutral, including anything else in the equation could put them out of reach. “If a drug were to reduce hospital admissions or length of hospital stay, including time spent in intensive care, this would be hugely beneficial to the health systems as it would free up capacity to treat more patients,” he said.

When the Coffers Are Empty but the Need Is Great

Sarah Garner, Honorary Professor, Division of Population Health, Health Services Research & Primary Care, Manchester University, Manchester, United Kingdom, agrees that it would be very helpful to consider alternative pricing approaches for wealthier countries, but stresses a different strategy again would be required for developing nations whose economies have been even more overwhelmed by the far-reaching impact of the coronavirus.

“We are seeing that many countries simply do not have anything left in the budget for COVID-19 treatment options so even providing medicines at a heavily discounted rate would not help them. Solidarity among all stakeholders to recognize the reality of the situation and a resolve to work jointly to bring this illness under control will be vital in the coming months. For example, research capacity and funding, voluntary licensing agreements, and patent pooling and coordination of supply will be essential,” Garner said.

She added that a coordinated global approach to the pandemic will be a vital part of helping even the poorest in the world to recover from this outbreak.

After the Virus Has Gone, What Then?

Grüeger believes it will be important to focus once again on striking a balance between rewarding innovation and ensuring the best care is made available within existing budgets once the world emerges from the pandemic.

But Garner, who has long argued that the prices of innovative medicines are preventing broad patient access even in high-income countries, thinks that COVID-19 could provide healthcare systems with the push they need to break free from a “dysfunctional status quo” and move towards new pricing and access models.

At the moment, many countries are simply capping the numbers of patients eligible for treatment with the latest scientific breakthroughs in order to control budgets, but this is depriving many people of important treatment options.

She believes the time has come for industry to accept lower prices—a move that will ultimately result in medicines reaching more people, thereby increasing sales volume. “At the moment, many countries are simply capping the numbers of patients eligible for treatment with the latest scientific breakthroughs in order to control budgets, but this is depriving many people of important treatment options. Pharmaceutical companies could still see healthy profits if they were to shift to a pricing strategies that also take volume into account,” she said.

“We have a chance to reconfigure the development and access pathways of new medicines that will drive equitable and timely access to life-changing and life-saving medicines while still providing incentives for innovation. COVID-19 is an unprecedented challenge that has expedited us through a lot of the conversations on problems, inefficiencies, costs being too high, and so on that have been going on for years. We are now seeing brilliant examples of how stakeholders are working together to reach common goals,” she said.

Tightening the Purse Strings

The ability of all countries to pay for the latest medicines looks set to become more limited in the coming years. Governments everywhere are currently spending billions of dollars in desperate attempts to prop up their ailing economies that, like their citizens, have fallen victim to the pandemic.

The implications for drug budgets that were already under considerable pressure due to years of austerity in the

wake of the 2008-2009 financial crisis will become clear once countries eventually recover from the pandemic.

“Governments and policymakers will have to make trade-off decisions about where they want to spend money. It’s about making sure they achieve maximum return on their investment in

innovation, prevention, and capacity,” Schröter said.

For Schröter this means the time has come for healthcare systems to get serious about embracing value-based healthcare. “COVID-19 could end up being to healthcare what 9/11 was to the defense sector. It could spur investment in new health technologies, infrastructure, and data. But the whole system needs to change, and the money we are spending needs to drive that change so that we emerge with a healthcare system that focuses on delivering better outcomes at lower cost to all stakeholders regardless of where in the value chain they are,” he said.

A results-focused and data-driven approach to healthcare delivery will enable a more holistic analysis of the cost-benefit profiles of different health interventions. Schröter said, “This will set out the right incentives so that companies invest in the areas that will deliver maximum value to their stakeholders.”

Valuing Health

Grüeger also believes that the pandemic has highlighted just how much citizens, governments, policymakers, investors, and other key stakeholders value health. “COVID-19 has shown us all that we value health a lot more than we thought. Governments have immediately stepped in to protect lives even at a huge cost to their economies. Once this pandemic is over, I do think that we will see a return to value-based pricing, but I think our definition of value will be much broader,” he said.

"This pandemic has shown us that people want medicines that deliver far more than clinical benefits; they want medicines that have an impact on broader societal issues as well. Take Alzheimer's disease for example. The indirect costs of this dreadful disease are huge so any medicine that can also address them will be incredibly beneficial for societies as a whole," he said.

Good health is fragile. The pandemic has made this clear to everyone.

It may well be that the newest innovations are initially only available to the countries that are willing to pay a price that will secure faster access to it, but broader access will ultimately follow, Schröter said. "I think we may end up seeing something that is similar to the 1960s Moon Challenge in the United States. Much of the cutting-edge technology that was designed to help America succeed made its way into our lives in the years that followed; the quality has remained the same but over time the prices have come down. As long as high-end pharmaceutical research and innovation are incentivized, breakthrough products will eventually reach more patients across the world. We need some countries to spearhead and reward this innovation. The worst outcome would be that the innovation does not happen in the first place."

Ensuring That Everyone Has Access to the Latest Medicines

Grüeger believes the pandemic may result in a greater willingness amongst countries to more formally and transparently adopt a tiered approach to the funding of innovation both during and after the pandemic. "Some countries, such as the United States, are clearly willing to pay a premium for innovation in order to ensure faster access to it. This was the case before the pandemic and we are seeing that it remains the case during the pandemic," he said. "The reality is that only high-income countries, such as the United States, Japan, Europe, and possibly China can afford to pay value-based prices for the most innovative products. For other countries, a cost-neutral approach may make more sense. Budget holders in less

wealthy countries will have to make a trade-off between incremental benefits, affordability, and how quickly they want to be able to access the medicine. We are already seeing that many countries are not willing to pay a premium to ensure faster access to the most innovative medicines," he said. "For lower income countries, a cost-based model would be the most appropriate way of ensuring that patients in these areas can access the latest medicines."

Garner agrees that COVID-19 might accelerate a more comprehensive evaluation of whether tiered pricing is a feasible way forward. She believes it could even result in companies revising their traditional launch sequences so that drugs come to more markets at the same time. This would result in governments and budget holders, rather than pharmaceutical companies, determining how quickly their citizens are able to access these medicines. "We may well see that tiered pricing gains in importance due to this infectious disease. We clearly need to make any medicines that could save people's lives and slow the spread of COVID-19 available around the world. There have been a number of companies that have taken a major step in this direction through the access agreements that are being put in place. This could provide a model for drug launches after the pandemic," she said.

Such a change could mark the beginning of a new order in terms of health ownership and the way decisions are made by all stakeholders.

Concurrent launches would mean that it would be possible for patients to access effective innovative therapies more quickly. Of course, availability of the medicine would still depend on budget holders' willingness and ability to pay. But this important shift could shake up the dynamic of healthcare discussions; citizens would be emboldened to hold policymakers, governments, and payers to account for their decisions about whether to fund the latest medicines.

Good health is fragile. The pandemic has made this clear to everyone. People are beginning to understand there is a lot they can do to determine their own health outcomes. They are also

becoming more aware that the job of policymakers and governments is to provide a functioning healthcare system; a system that makes it possible for doctors and nurses to deliver the care people need when their health fails. A key element of this will be to make sure effective medicines are available. Prices of medicines are one very important part of the equation, but access will require that all parts of the equation are balanced. ■

References

1. COVID-19 situation update worldwide, as of 21 November 2020. <https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases>; accessed November 20, 2020.
2. A Long, Uneven and Uncertain Ascent; <https://blogs.imf.org/2020/10/13/a-long-uneven-and-uncertain-ascent/>. Accessed November 20, 2020.
3. Remdesivir coronavirus treatment will eventually need a "sustainable model" to keep it accessible, Gilead CEO says. <https://www.cnbc.com/2020/05/01/coronavirus-remdesivir-will-need-a-sustainable-model-gilead-ceo-says.html>. Accessed June 14, 2020.
4. An Open Letter from Daniel O'Day, Chairman & CEO, Gilead Sciences. <https://www.gilead.com/news-and-press/press-room/press-releases/2020/6/an-open-letter-from-daniel-oday-chairman-ceo-gilead-sciences>. Accessed June 15, 2020.
5. Coronavirus: Johnson & Johnson vows to make "not-for-profit" vaccine. <https://news.sky.com/story/coronavirus-johnsonjohnson-vows-to-make-not-for-profit-vaccine-11966292>. Accessed June 15, 2020.
6. AstraZeneca to supply Europe with up to 400 million doses of Oxford University's vaccine at no profit. <https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2020/astrazeneca-to-supply-europe-with-up-to-400-million-doses-of-oxford-universitys-vaccine-at-no-profit.html>. Accessed June 15, 2020.
7. GSK actions to support the global response to COVID-19. https://www.gsk.com/media/5978/coronavirus_factsheet_2.pdf. Accessed June 15, 2020.
8. 9 Pharmaceutical Companies Racing for A COVID-19 Vaccine. <https://www.forbes.com/sites/moneyshow/2020/06/16/9-pharmaceutical-companies-racing-for-a-covid-19-vaccine/?sh=5265e96276ad>. Accessed June 16, 2020.

The Evaluation of Pivotal Trials for Advanced Therapies From Regulatory and Health Technology Assessment Perspectives in Europe

Tingting Qiu, PhD, Aix-Marseille University, Marseille, France; Monique Dabbous, PhD, Aix-Marseille University, Marseille, France; Borislav Borissov, PhD, Prescripta, Sofia, Bulgaria

Pivotal studies for approved advanced therapies have been evaluated by health technology assessment bodies in major European countries with an aim to enlighten the design of future advanced therapy trials.

The novelty and complexity of advanced therapies have raised barriers in their development as well as challenges at regulatory and market access levels. Clinical trials for advanced therapies are typically open-label, single-arm trials with small sample sizes and short follow-up durations. Inconsistencies were identified between regulators and payers in terms of acceptance of such short-term noncomparative clinical evidence for advanced therapies. The uncertainty relating to the evidence for these therapies should be sufficiently addressed to satisfy the expectations of both parties at the time of launch.

Pivotal studies for approved advanced therapies have been evaluated by health technology assessment (HTA) bodies in major European countries with an aim to enlighten the design of future advanced therapy trials.

Enhanced interactions between regulators and HTA bodies are needed to reach an agreement on the evidence requirements for not only pivotal clinical trials, but also for postmarketing evidence-generation requirements to be fulfilled.

Challenges in the Clinical Trials for Advanced Therapy Medicinal Products

Advanced therapy medicinal products (ATMPs) hold great potential to transform the conventional paradigm of disease management by targeting the underlying causes of the diseases. ATMPs represent significant promises for rare genetic disorders lacking alternative treatment. Due to the unique and complex nature of ATMPs, they are associated with challenges at the manufacturing and clinical development levels as well as significant hurdles to achieving market access. In particular, conducting conventional randomized clinical trials to collect reliable and robust evidence could be more challenging for ATMPs than for traditional drugs. As most ATMPs target rare disorders,¹ they will face the

same challenges associated with orphan drugs. The small target population of ATMPs leads to difficulties with regards to patient recruitment and conducting head-to-head studies. Most rare genetic diseases have no curative treatments, which requires patients to rely on symptomatic treatments and results in great variations in the standard of care.² Blinding patients and/or physicians seems impractical due to novel methods of administration and the unique safety profiles of ATMPs. In addition, patients have expressed hesitations to participate in blinded clinical trials with a placebo or less effective standard of care when an active therapy, especially with a potential for cure, may be available.³ This has also been cited as a reason for failure in patient recruitment for several COVID-19 studies as active treatments could be made available through other paths.⁴ Furthermore, ATMP clinical trials are required to be conducted only in authorized centers with adequate infrastructures for the administration and management of ATMPs. This increases patient burden of traveling to trial sites and may also result in potential selection bias towards patients able to endure traveling.⁵

Differences Between Regulators and Payers in the Evidence Requirements for ATMPs

Regulation EC No 1394/2007 on ATMPs introduced a more flexible approach for the assessment of quality, safety, and efficacy evidence of an ATMP taking into consideration the novelty, complexity, and technical specificity of ATMPs. Moreover, ATMPs represent therapeutic advantages in addressing the unmet clinical needs for devastating conditions; thus ATMPs are highly likely to be eligible for expedited pathways, such as conditional marketing authorization and Priority Medicine designation.⁶ This translates into an increased approval rate of ATMP despite nonconventional studies, such as single-arm trials and very small sample size studies in ultrarare conditions (Table 1). Regulators have shown a willingness

Table 1. Study methodology of pivotal studies for ATMPs submitted for market authorization and HTA.

Brand name	Study name	Study design	Follow-up duration at the time of MA	Sample size	Primary efficacy endpoints
Glybera®	1. CT-AMT-011-01	Phase 2/3, multicenter, single arm, open-label, dose-escalation study	3 months	15	Reduction of fasting TG concentrations
	2. CT-AMT-011-02	Phase 2/3, multicenter, single arm, open-label, single-dose study	4.5 months	5	Reduction of fasting TG concentrations
Imlygic®	Study 005/05	Phase 3, multicenter, randomized, controlled, open-label study. Comparator: GM-CSF	17.1 months	436	Durable response rate
Alofisel®	Cx601-0302 study (ADMIRE-CD study)	Phase 3, multicenter, randomized, double-blinded, placebo-controlled study	6 months (extension to 26 months)	208	Combined remission of perianal fistulizing CD and absence of collections > 2 cm of the treated fistula confirmed by MRI images
Zalmoxis®	TK007 study	Phase 1/2, multicenter, single arm, open-label, interventional studies	36 months	30	The proportion of patients who achieved immune reconstitution
	TK008 study	Phase 3, multicenter, randomized, controlled, open-label study. HSCT+ Zalmoxis® versus HSCT alone	12 months	152	Proportion of patients who achieved immune reconstitution
Strimvelis®	AD1115611	Phase 1/2, multicenter, single arm, open-label, interventional studies	36 months	12	Survival
Provenge®	D9902B (IMPACT)	Phase 3, multicenter, randomized, double-blinded, placebo control study	60 months	512	Overall survival
Luxturna®	Study 301	Phase 3, multicenter, randomized, open-label, control study. Comparator: SoC	12 months	31	Multi-luminance Mobility Testing (MLMT), bilateral
Yescarta®	ZUMA-1 study	Phase 1/2, multicenter, single arm, open-label study	12 months	101	Overall response rate
Kymriah®-B cell ALL	1. ELIANA-BB2202 study	Phase 2, multicenter, single arm, open-label study	13.1 months	92	Overall remission rate
	2. ENSIGN study	Phase 2, multicenter, single arm, open-label study	6 months	64	Overall remission rate
Kymriah®-DLBCL	JULIET-study C2201	Phase 2, multicenter, single arm, open-label study	11.4 months	147	Overall response rate

ALL indicates acute lymphoblastic leukemia; CD=Crohn's disease; DLBCL=diffuse large B-cell lymphoma; GM-CSF=granulocyte-macrophage colony-stimulating factor; HSCT=hematopoietic stem cell transplantation; MA=market authorization; MRI=magnetic resonance imaging; SoC=standard of care; TG=triglyceride.

to grant access to this new class of pharmaceuticals based on favorable benefit-risk balances despite the magnitude of the benefits remaining difficult to quantify due to short-duration single-arm studies and the frequent use of surrogate outcomes.

In contrast to regulators' enthusiasm to facilitate the timely marketing authorization based on limited evidence, HTA bodies hold more conservative attitudes towards ATMPs. HTA bodies concluded that limited clinical evidence increased the uncertainties surrounding the curative potential, the magnitude and

the durability of clinical benefits, and the potential unfavorable effects in the long run. Consequently, the determination of value as well as justification of the high treatment cost relative to its value seemed inconclusive, rendering payers reluctant or hesitant to reimburse ATMPs within constrained budgets.⁷ Furthermore, there are disparities in evidence requirements for HTAs; for example, the acceptance of indirect comparisons and the methods for heterogeneity adjustments may differ across HTA bodies.

The methodology of clinical trials for

ATMPs was the primary cause for reserved opinions of HTA bodies about ATMP. It is interesting to analyze how approved ATMPs have been assessed in order to identify where efforts could be implemented to increase the chances of positive recommendations by HTA bodies for future ATMPs.

Uncertainties in the Pivotal Evidence for Approved ATMPs

Based on the HTA outcomes for approved ATMPs in selected European countries (England, Scotland, France, Germany, and Sweden), the key limitations of clinical evidence for ATMPs

were identified to be due to study design, study population, study endpoints, statistical analysis methods, confounding factors, and indirect comparisons.

The design of pivotal studies for ATMPs was the most frequently criticized by HTA bodies, including the single-arm trial design, small sample size, short follow-up duration, high dropout rate, and discordance between the dosage regimen in the clinical trials and the marketing authorization. Regarding comparative studies, limitation was associated with the comparator selection, which was either not considered as the standard of care or it was no longer applied in clinical practice, making it difficult for the HTA body to appreciate the ATMP value.

Enhanced interactions between regulators and HTA bodies are needed to reach an agreement on the evidence requirements for not only pivotal clinical trials, but also for postmarketing evidence-generation requirements to be fulfilled.

The main issues related to the study population were discrepancies between the patients recruited in the clinical trials and the marketing authorization label, the exclusion of patients with a higher disease severity in the trial, and the lack of representation of the study population to the treatment-eligible population.

The limitations of the study endpoints were mainly the use of surrogate endpoints as primary endpoints, the clinical relevance and the validity of primary endpoints in the real-world setting, analysis on a posthoc basis but not prespecified, and the reliability of endpoints due to the intertest variability.

The statistical analysis methodologies presented limitations with regards to the following: incomplete information on the imputation procedure for missing values; unreliable survival extrapolation based on short-term clinical evidence; uncertainty in the estimation of the long-term survival using the Kaplan-Meier method; and potential overestimation of treatment benefits resulted from full analysis set analysis rather than intention to treat analysis.

The presence of confounding factors that may bias the treatment benefits estimated could not be ruled out in several cases. This mainly included the impact of dietary regime on treatment effect, long waiting periods and bridging treatment prior to randomization, imbalance in patient characteristics and withdrawal rates between 2 comparison groups, and the questionable appropriateness of pooling data from heterogeneous studies.

The challenges in the transferability and generalizability of clinical data were criticized, mainly around the disparity between the treatment pathways adopted in the study and real-world clinical practice and the extrapolation of short-term clinical evidence for long-term treatment benefits.

Indirect comparison was generally derived using data from systematic reviews and meta-analyses, historical comparisons, patient registries, or network databases. The main limitations of indirect comparisons were indicated in the heterogeneity of patient characteristics, differences in the outcomes investigated, potential biases due to uncontrolled confounding factors, and the difficulties to draw firm conclusions regarding relative effectiveness comparing with historical observational studies of flawed methodology. The inherent limitations for studies utilizing indirect comparison included small patient populations, incomplete information about baseline patient characteristics, inability to trace retrospective studies, and the potential selection bias for studies included in meta-analyses.

Future Insights for Comprehensive Evidence Collection

Considering the substantial number of potentially transformative ATMP marketing authorization applications in the next years, regulators realized the urgency to provide more clarification on regulatory requirements in order

to support ATMP developers in early clinical trial design. Earlier this year, the US Food and Drug Administration released a series of guidelines on the recommendations for specific diseases with a large number of products in development, such as guidance on gene therapy for hemophilia, retinal disorders, and Sanfilippo Syndrome. However, there are no specific HTA guidelines for ATMP development. Because HTA bodies offer a limited number of early advices to help developers in the clinical development plan preparation, HTA guidelines providing clearly defined requirements on the study methodology and economic assessment would be embraced by developers to better prepare the HTA dossiers.

Moreover, both regulators and HTA bodies emphasized the need for post-launch evidence generation to bridge the evidence gap with initial assessments of ATMPs. Regulators expect post-launch evidence to confirm positive benefit-risk balances as claimed, while HTA bodies will utilize it for subsequent price negotiations and decisions on the continuation or termination of performance-based payments. Post-launch follow-up studies are conducted for almost all approved ATMPs to assess the long-term effectiveness and safety. However, study designs of these post-launch studies generally have resembled those of pre-approval studies in terms of strict inclusion criteria and the small number of patients to be enrolled.⁸ This has raised skepticism regarding whether such postlaunch studies will be sufficient for HTA bodies to provide confirmatory evidence on the actual treatment benefits of ATMPs in real-world scenarios.

Next Steps

Enhanced interactions between regulators and HTA bodies are needed to reach an agreement on the evidence requirements for not only pivotal clinical trials, but also for postmarketing evidence-generation requirements to be fulfilled. Additionally, further efforts are needed in standardizing the methodology to collect, report, and analyze the data from postmarketing observational studies in order to mitigate inherent limitations. Centralized disease or product registries, instead of numerous protocols from individual

companies developing ATMPs with similar mechanisms of action, will be valuable to streamline the evidence collection and improve the quality of postmarket data. •

References

1. Lapteva L, Vatsan R, Purohit-Sheth T. Regenerative medicine therapies for rare diseases. *Transl Sci Rare Dis*. 2018;3:121-132.
2. Abrahamyan L, Feldman BM, Tomlinson G, et al. Alternative designs for clinical trials in rare diseases. *Am J Med Genet C Semin Med Genet*. 2016;172:313-331.
3. Gaasterland CMW, van der Weide MCJ, du Prie-Olthof MJ, et al. The patient's view on rare disease trial design-a qualitative study. *Orphanet J Rare Dis*. 2019;14:31.
4. Joseph A. Efforts to beat back the coronavirus are critical. They're also making clinical trials harder. 2020. <https://www.statnews.com/2020/05/05/efforts-to-beat-back-the-coronavirus-are-critical-theyre-also-making-clinical-trials-harder/>
5. The full reference is: White W. A rare disease patient/caregiver perspective on fair pricing and access to gene-based therapies. *Gene Therapy*. 2020;27:474-481.
6. European Union. Regulation (EC) No. 1394/2007 of the European Parliament and of the Council of 13 November 2007. On advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. *Official J Eur Union*. 2007;(L324)121.
7. Ermisch M, Buccics A, Vella Bonanno P, et al. Payers' views of the changes arising through the possible adoption of adaptive pathways. *Front Pharmacol*. 2016;7:305.
8. Fritsche E, Elsallab M, Schaden M, et al. Post-marketing safety and efficacy surveillance of cell and gene therapies in the EU: A critical review. *Cell Gene Ther Insights*. 2019;5:1505-1521.

You know HEOR, but how well does the HEOR community know you?



Whether you're providing research acumen or training, looking to attract talent to your organization, or trying to gain access to decision makers in this market, ISPOR is your connection to the global HEOR community.

Discover the various ways to advertise and partner with ISPOR—your unparalleled link to the influential audience of 30,000+ HEOR professionals.

For more information, please contact us at advertise@ispor.org.



Regulatory Pathways in Europe, the United States, and Japan and Health Technology Assessments for Gene Therapies

Yitong Wang, PhD, Aix-Marseille University, Marseille, France; Tingting Qiu, PhD, Aix-Marseille University, Marseille, France; Shuyao Liang, PhD, Aix-Marseille University, Marseille, France; Claude Dussart, PhD, Université Claude Bernard Lyon 1, Lyon, France

Variations still exist in marketing authorization pathways and expedited approval programs for gene therapies across Europe, the United States, and Japan due to the different regulatory environments and public health needs.

Over the past few years, several gene therapies have been approved and adopted in many countries and a substantial number of them are in the pipeline.¹ The US Food and Drug Administration (FDA) is expecting to receive more than 200 investigational new drug applications per year, and, by 2025, to approve 10 to 20 cell and gene therapies per year.² However, considering the uncertainty of long-term clinical evidence and the high prices associated with gene therapies, transitioning such new advances from the bench to the bedside is often challenging.^{3,4} This paper provides an overview of cell and gene therapies, marketing-authorization pathways in the European Union (EU), the United States, and Japan. Additionally, the regulatory and reimbursement status of gene therapies were compared in the United States and 5 European countries: France, the United Kingdom (England and Scotland), Germany, Italy, and Spain.

Marketing Authorization Pathways and Expedited Approval Programs

Authorities in Europe, the United States, and Japan have developed various expedited approval programs (Table 1). These adaptive regulatory pathways aim to accelerate the market approval of gene therapies and vary to a great degree between the 3 authorities.

In the European Union, gene therapies (defined as advanced therapy medicinal products [ATMPs]) are regulated like other pharmaceuticals through a centralized marketing authorization procedure to ensure a single evaluation and authorization decision applicable to all EU countries (Figure 1). The Committee for Advanced Therapies assesses the quality, safety, and efficacy of gene therapies based on the marketing authorization application submitted by the manufacturers and prepares a draft opinion on

Figure 1. Gene therapies, regulatory pathways in Europe and Japan

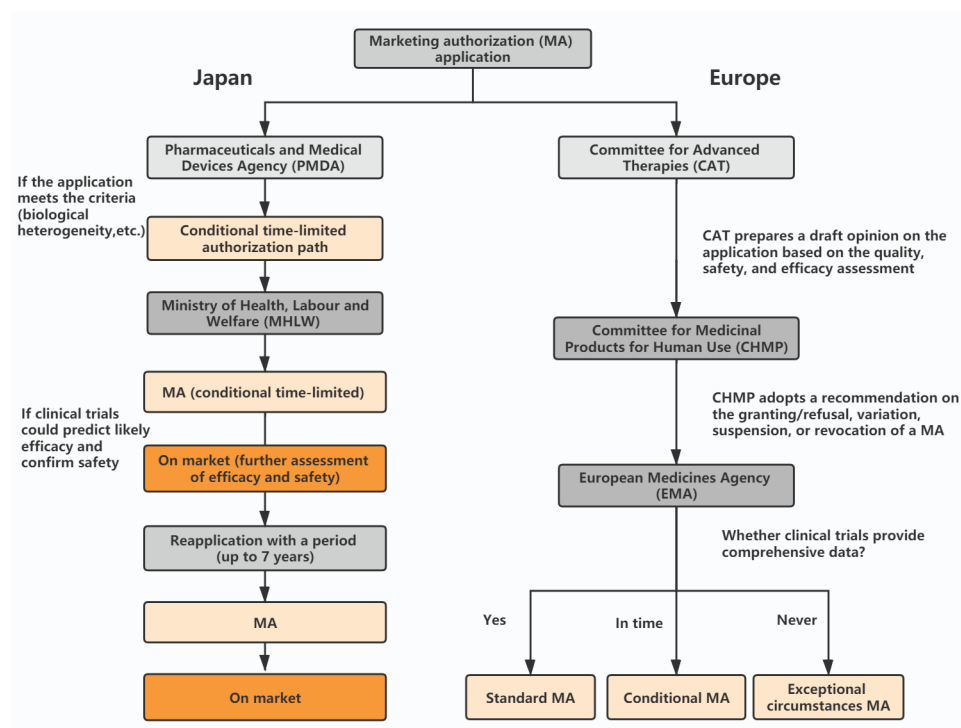


Table 1. The marketing authorization regulation agencies and Expedited programs in Europe, the United States, and Japan

Country	Regulation agency	Specific committee	Expedited programs
United States	US Food and Drug Administration	Center for Biologics Evaluation and Research;	Fast track: it is a process designed to facilitate the development- and expedite the review of drugs to treat serious conditions and fill an unmet medical need
		Office of Tissue and Advanced Therapies	Breakthrough therapy designation: a process designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy
		Cellular, Tissue, and Gene Therapies Advisory Committee	Regenerative medicine advanced therapy designation: it includes all the benefits of the fast track and breakthrough therapy designation programs, including early interactions with FDA
		Tissue reference group	Priority review designation: it means FDA's goal is to take action on an application within 6 months.
European Union	European Medicines Agency	Committee for Advanced Therapies	Conditional market authorization: it is for such medicines that address unmet medical needs where the benefit of immediate availability outweighs the risk of less comprehensive data than normally required
			Approval under exceptional circumstance: it is an MA in absence of comprehensive data that cannot be obtained even after authorization
			Priority medicine (PRIME) designation: it is a scheme launched by EMA to enhance support for the development of medicines that target an unmet medical need.
Japan	Ministry of Health, Labour and Welfare	Pharmaceuticals and Medical Devices Agency	Time limited, conditional market authorization: it is a maximum of 7 years, MA on condition that further data will be collected during a conditional MA period
		Cellular and tissue-based products subcommittee	SAKIGAKE designation: it is a program that aims to encourage and accelerate the practical application of innovative drugs for serious and life-threatening diseases
			Regenerative medicine specific orphan drug designation: it allows subsidy granting of direct expenses of the development and authorization of orphan products indicated for serious disease with high medical needs
			Priority review: it means PMDA review time is reduced to 9 months compared to 12 months under standard review

MA indicates marketing authorization; US=United States; FDA=Food and Drug Administration; EMA=European Medicines Agency; PMDA=Pharmaceuticals and Medical Devices Agency

the application. The Committee for Medicinal Products for Human Use reviews the recommendations from the Committee for Advanced Therapies and adopts a final opinion on the marketing authorization decision. Apart from the standard marketing authorization pathway, conditional marketing authorization and marketing authorization under exceptional circumstances are also established. Gene therapies are eligible for conditional marketing authorization if they have a positive benefit-risk balance and are likely to satisfy unmet medical needs. The marketing authorization holders must fulfill the scientific obligations to submit the postmarket confirmatory evidence before the conditional marketing authorization may be converted into a standard marketing authorization. Unlike the conditional marketing authorization, the marketing authorization under exceptional circumstances is granted

when comprehensive data could not be possible to generate due to the disease rarity or unethical considerations.

In Japan, gene therapies (classified as regenerative medicines) are regulated by the Ministry of Health, Labour, and Welfare (MHLW) under a specific, unique, fast-track approval framework different from all other pharmaceuticals (Figure 1). The new legislative framework was proposed by the Act on the Safety of Regenerative Medicine (RM Act) and the Pharmaceuticals and Medical Devices Act (PMD Act) in November 2013, aiming at expediting the development and marketing authorization of regenerative medicines in Japan. A conditional time-limited marketing authorization may be issued by the Pharmaceuticals and Medical Devices Agency (PMDA) based on preliminary clinical trials indicating likely efficacy and confirmed safety. However, the marketing authorization

holders must submit a second application to the PMDA within a pre-defined period (with a maximum of 7 years), in order to reassess whether the regenerative medicines meet the requirements for standard marketing authorization based on postmarketing evidence. In Japan, for products targeting serious or life-threatening diseases without effective or available treatment, "SAKIGAKE" designation is proposed by the MHLW to encourage industry involvement in innovative products and to promote the marketing authorization ahead of other countries. The SAKIGAKE-designated drugs also benefit from prioritized consultation, accelerated review time, extended re-examination period, and premium pricing.

In the United States, gene therapies are classified under human cells, tissues, and cellular- and tissue-based products (HCT/P's) and are regulated as drugs

Table 2. Marketing authorization of gene therapy in European Union and the United States

Brand name	International non-proprietary name	Country	Market authorization pathway	MA date	Marketing authorization indication
Glybera	Alipogene tiparovec	EU	Familial lipoprotein lipase deficiency	10/25/2012	Approval under exceptional circumstance
Imlygic	Talimogene laherparepvec	EU	Unresectable melanoma	12/16/2015	Standard approval; additional monitoring
		US		10/27/2015	Fast track
Strimvelis	Autologous CD34+ cells transduced to express ADA	EU	Severe combined immunodeficiency due to ADA deficiency	5/26/2016	Standard approval; additional monitoring
Yescarta	Axicabtagene ciloleucel	EU	• Relapsed or refractory diffuse large B-cell lymphoma	8/23/2018	PRIME
		US	• Primary mediastinal large B-cell lymphoma after 2 or more lines of systemic therapy	10/18/2017	Breakthrough therapy designation; priority review
Luxturna	Voretigene neparovec	EU	Adult and pediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells	11/22/2018	Under additional monitoring; orphan designation
		US		12/19/2017	Breakthrough therapy designation; priority review
Kymriah	Tisagenlecleucel	EU	• Pediatric and young adult patients up to 25 years of age with B cell acute lymphoblastic leukemia (ALL) that is refractory, in relapse post transplant or in second or later relapse	8/22/2018	PRIME
		US	• Adult patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL) after 2 or more lines of systemic therapy	8/30/2017 (ALL); 4/13/2018 (DLBCL)	Breakthrough therapy designation; priority review
Zolgensma	Onasemnogene ABEPRVVEC-XIOI	EU	Pediatric patients less than 2 years of age with spinal muscular atrophy with biallelic mutations in the survival motor neuron 1 (SMN1) gene	5/18/2020	Conditional marketing authorization; additional monitoring
		US		5/24/2019	Breakthrough therapy designation; priority review

INN=International non-proprietary name; PRIME=Priority medicine; MA=Marketing authorization; ADA=Adenosine deaminase; EU=Europe; US=United States

and/or biological products by the Center for Biologics Evaluation and Research. A conditional approval pathway similar to the fast-track framework in Japan, was proposed in the REGROW Act by the FDA in March 2016, which sought to eliminate phase III studies to create an expedited approval pathway accepting less comprehensive evidence of safety and effectiveness. However, the REGROW Act was opposed by the academic community out of concern that the lower standards for marketing authorization would allow ineffective and possibly unsafe products to reach the market. A new accelerated approval pathway for regenerative medicines, known as Regenerative Medicine Advanced Therapy (RMAT) designation, was introduced in the 21st Century Cures Act in December 2016, with the intention to incentivize the development and marketing authorization of regenerative

medicines addressing unmet medical needs for serious or life-threatening disease. An additional 4 expedited programs for drugs that target to serious diseases especially without available treatments exist in the United States, including the fast-track designation, breakthrough therapy designation, accelerated approval, and priority review designation.

HTAs for Gene Therapies

To date, 7 gene therapies were approved in the European Union and/or the United States, among which alipogene tiparovec (Glybera) marketing authorization was withdrawn by the developing company due to commercial reasons (Table 2).^{5,6} The HTA decisions for gene therapies from 5 European countries are summarized in Table 3. Unlike many countries with official HTA agencies, the United States does not

have a national and formal HTA body to evaluate the technologies and make recommendations for reimbursement and pricing. The Institute for Clinical and Economic Review (ICER), founded in 2006, was an independent nonprofit organization to evaluate the clinical and economic value of the technologies, which has become very popular and influential on the United States healthcare system.

In the United States, ICER recognized that tisagenlecleucel (Kymriah), axicabtagene ciloleucel (Yescarta), and voretigene neparovec (Luxturna) offered a net health benefit despite uncertainty related to their evidence. ICER considered tisagenlecleucel and axicabtagene ciloleucel cost-effective within the context of a threshold of \$150,000 per quality-adjusted life year (QALY) gained in the United States.

Table 3. Marketing authorization of gene therapy in European Union and the United States

	France	Germany	UK-NICE	UK-SMC	Spain	Italy
Glybera	Not recommended	Recommended	NA	NA	NA	NA
Imlygic	NA	Not Recommended	Recommended with restriction of indication	Not recommended	Not recommended	NA
Strimvelis	NA	NA	Recommended	NA	NA	Recommended
Yescarta	Recommended	Recommended	Recommended within CDF	Recommended	Recommended	Recommended
Luxturna	Recommended	Recommended	Recommended	NA	NA	NA
Kymriah-DLBCL	Recommended	Recommended	Recommended within CDF	Recommended	Recommended	Recommended
Kymriah-B cell ALL	Recommended	Recommended	Recommended within CDF	Recommended	NA	Recommended
Zolgensma	NA	NA	NA	NA	NA	NA

B cell ALL indicates B-cell acute lymphoblastic leukemia; CDF=Cancer Drugs Fund; DLBCL=diffuse large B-cell lymphoma; NA=not available; NICE=National Institute for Health and Care Excellence; SMC=Scottish Medicine Consortium.

These therapies seemed to be priced in alignment with clinical benefits over a lifetime time horizon according to ICER's evaluation.⁷

In France,⁸ 3 gene therapies, axicabtagene ciloleucel (Yescarta), voretigene neparvovec (Luxturna), and tisagenlecleucel (Kymriah), were recommended for reimbursement by the French National Authority for Health (HAS), which were all considered to demonstrate an important actual clinical benefit (*Service medical rendu* [SMR]: important). Alipogene tiparvovec (Glybera) was not recommended by the HAS and was considered to have insufficient medical benefit due to heterogeneity of effectiveness, uncertainty of safety, and limitations of methodology.

In Germany,⁹ only talimogene laherparepvec (Imlygic) was attributed to have no added benefit due to the use of inappropriate comparator from the Federal Joint Committee's perspective. Three gene therapies, alipogene tiparvovec (Glybera), tisagenlecleucel (Kymriah), and axicabtagene ciloleucel (Yescarta), were granted non-quantifiable additional benefit. A fourth gene therapy, voretigene neparvovec (Luxturna), was recognized as providing a considerable added benefit. All 4 gene therapies, recommended by the German Institute for Quality and Efficiency in Health Care, are orphan drugs, which are automatically granted an additional

benefit by law irrespective of the available clinical evidence.

In England,¹⁰ the National Institute for Health and Care Excellence (NICE) has recommended the reimbursement of talimogene laherparepvec (Imlygic) in the restricted subgroup population with best responses. Tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta) were approved for use within the Cancer Drugs Fund while further data collection is ongoing. Autologous CD34+ cells transduced to express ADA (Strimvelis) was recommended by NICE for its clinical benefits in improving survival and its cost-effectiveness below the threshold for highly specialized technologies at £100,000 per QALY gained. In Scotland,¹¹ tisagenlecleucel for 2 indications and axicabtagene ciloleucel were recommended for reimbursement by the Scottish Medicine Consortium with patient access schemes.

Three gene therapies, axicabtagene ciloleucel (Yescarta), voretigene neparvovec (Luxturna), and tisagenlecleucel (Kymriah) were recommended by the Italian Medicines Agency¹² in Italy with managed entry agreements. Two gene therapies, axicabtagene ciloleucel (Yescarta) and tisagenlecleucel, were recommended to be used in authorized centers in Spain.¹³

Translation Insights

Substantial efforts have been made by regulators to accelerate the assessment and approval of transformative gene

therapies.¹⁴ Variations still exist in marketing authorization pathways and expedited approval programs for gene therapies across the European Union, the United States, and Japan due to the different regulatory environments and public health needs. Enhanced international coordination is recommended to standardize the marketing authorization requirements, in order to minimize duplicated work and to facilitate the availability of gene therapies globally.

After marketing authorization, patient access to gene therapies ultimately depends on decisions made by payers and HTA organizations. Payers need to maintain a balance between ensuring access to medical innovation and encouraging sustainable development of cell and gene therapy.¹⁵ Various approaches have been adopted by different countries to mitigate the potential risk of reimbursing gene therapies with substantial uncertainties surrounding long-term outcomes.¹⁶ Payers generally have expressed openness to such innovation. However, it is questionable how they will react and deal with the continuously increasing number of gene therapies seeking market access. •

References

1. Qiu T, Dabbous M, Borislav B, Toumi M, Hanna E. Health technology assessment of gene therapies in Europe and the USA: Analysis and future considerations. *Cell Gene Ther Insights*. 2019;5:1043-1059.

2. Statement from FDA Commissioner Scott Gottlieb, MD and Peter Marks, MD, PhD, Director of the Center for Biologics Evaluation and Research on new policies to advance development of safe and effective cell and gene therapies. US Food and Drug Administration. <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-peter-marks-md-phd-director-center-biologics>. Accessed June 28, 2020.
3. Ilic N, Savic S, Siegel E, Atkinson K, Tasic L. Examination of the regulatory frameworks applicable to biologic drugs (including stem cells and their progeny) in Europe, the U.S., and Australia: part I—a method of manual documentary analysis. *Stem Cells Transl Med*. 2012;1(12):898-908.
4. Witten CM, McFarland RD, Simek SL. Concise Review: The US Food and Drug Administration and regenerative medicine. *Stem Cells Transl Med*. 2015;4(12):1495-1499.
5. Approved cellular and gene therapy products. US Food and Drug Administration <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products>. Accessed July 24, 2020.
6. European Medicines Agency. <https://www.ema.europa.eu/en>. Accessed June 20, 2020.
7. Institute for Clinical and Economic Review report finds costs of approved CAR-T therapies align with clinical benefit. <https://icer.org/pressreleases/car-t-evidence-report/>. Accessed June 20, 2020.
8. French health authority. <https://www.has-sante.fr/portail/>. Accessed June 20, 2020.
9. Institute for Quality and Efficiency in Health Care. <https://www.iqwig.de/en/home.2724.html>. Accessed June 20, 2020.
10. The National Institute for Health and Care Excellence. <https://www.nice.org.uk/>. Accessed June 20, 2020.
11. Scottish Medicine Consortium. <https://www.scottishmedicines.org.uk/>. Accessed June 20, 2020.
12. The Italian Medicines Agency. <https://www.aifa.gov.it/>. Accessed June 20, 2020.
13. Agencia de Evaluación de Tecnologías Sanitarias. <http://www.isciii.es/>. Accessed June 20, 2020.
14. FDA. FDA's Efforts to Advance the Development of Gene Therapy. <https://www.fda.gov/news-events/fda-voices/fdas-efforts-advance-development-gene-therapy>. Accessed June 20, 2020.
15. Barlow JF, Yang M, Teagarden JR. Are payers ready, willing, and able to provide access to new durable gene therapies? *Value Health*. 2019;22(6):642-647.
16. Hanna E, Toumi M, Dussart C, et al. Funding breakthrough therapies: A systematic review and recommendation. *Health Policy*. 2018;122(3):217-229.

How to Make an Impact on Healthcare Decision Making? Develop an ISPOR Good Practices Task Force Proposal

Marc L. Berger, MD, ISPOR Special Advisor for Real World Evidence

As Value & Outcomes Spotlight evolves into a more digitally focused format, we will be introducing complementary online content, and we begin that transformation with a video interview that is a companion piece to this article. In the video interview, Editor-in-Chief Zeba Khan spoke to Dr Berger about his work on ISPOR task forces, his long illustrious career, and even offered some advice for new professionals. That conversation is featured in the accompanying video, which you can access [here](#).



The Value and Importance of ISPOR Good Practices Task Force Reports

ISPOR's Good Practices Task Force Reports are highly cited, multistakeholder-perspective expert guidance reports that reflect international standards for health economics and outcomes research (HEOR) and their use in healthcare decision making. From 2003 through 2019, ISPOR has published more than 60 [Good Practices Task Force Reports](#) covering a variety of methods, including patient preference measurement, indirect treatment comparisons and network meta-analyses, prospective and retrospective observational studies, decision analytic modeling, economic evaluation, and clinical outcomes assessment.

These reports have been cited by regulatory and health technology assessment agencies in the United States, Canada, Germany, France, The Netherlands, Brazil, and others. Other organizations, such as the Academy of Managed Care Pharmacy, European Network for Health Technology Assessment, the US Food and Drug Administration (FDA), and the [Equator Network](#) cite multiple ISPOR Good Practices Task Force Reports. Furthermore, the *Journal of the American Medical Association (JAMA)* and the International Committee of Medical Journal Editors recommend the Equator Network guidelines that include [Consolidated Health Economic Evaluation Reporting Standards \(CHEERS\) Statement](#) and 3 other ISPOR Good Practices Task Force Reports, in their instructions to authors.

The ISPOR Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness Report¹ was cited in Framework for FDA's Real-World Evidence Program.² This particular report has been part of a bigger ISPOR effort to address a recurring topic in [ISPOR's Top 10 Healthcare Trends Report](#): real-world evidence (RWE) in healthcare decision making. Thus, these efforts have been a cornerstone in support of ISPOR's mission: "To promote health economics and outcomes research excellence to improve decision making for health globally."

ISPOR has also been involved in translating regulatory guidance into practical recommendations for trial sponsors and other stakeholders. ISPOR has published 11 ISPOR Patient-Reported Outcomes/Clinician Outcomes Assessment Good Practices Task

Force Reports that provide recommendations based on the FDA's PRO Guidance for Industry.³ Two more related task forces are currently underway: the [Performance Outcome Assessments](#) and [Measurement Comparability of Patient-Reported Outcomes Measures](#).

What Issues Do ISPOR Good Practices Reports Address?

ISPOR Good Practices Task Forces serve several purposes. They can represent consensus guidance on the appropriate methods, analysis, and reporting standards to conduct research to inform healthcare decisions and improve health. They can provide specific recommendations on the design and approach for conducting research, how analyses should be performed, and how the results from HEOR should be interpreted and disseminated. At their very simplest, these task force reports can provide a roadmap for the reader to follow on how to accomplish the desired result.

The reports address areas of agreement, as well as issues where there are gaps or controversies that have not been resolved or integrated in the HEOR literature. The reports can address topics for which there is little or no published guidance (eg, patient-reported outcome and observer-reported outcome assessment in rare disease clinical trials and clinician-reported outcomes) or methods from other fields now applied to healthcare (eg, dynamic simulation-modeling methods in healthcare delivery research and health preference methods research). In this case, the reports are designated as ISPOR Emerging Good Practices Task Force Reports. This specific type of reports describes "the developing state of the art," identifies issues that require additional research and development, as well as makes some provisional recommendations.

Why and How to Get Involved

Any ISPOR member can develop a task force proposal.⁴ Indeed, most task force proposals have been initiated by one or more ISPOR members based on their own judgment of the need for expert guidance on a given topic. For example, several *Value in Health* reviewers initiated proposals after repeatedly seeing incorrect analyses on discrete choice experiments and mapping health-state utilities from nonpreference-based outcomes measures.

Personally, I have initiated 3 task forces and actively participated in 6 altogether; they have been among the most satisfying experiences of my career. Most recently, I instigated an effort to formally propose the registration of real-world data studies of treatment and/or comparative effectiveness. This quickly evolved into a collaborative effort with the International Society of Pharmacoepidemiology (ISPE), the Joint ISPE/ISPOR Special Task Force³ resulting in joint publication of 2 reports in *Value in Health* and *Pharmacoepidemiology and Drug Safety*.

Mid-career members are encouraged to consider developing task force proposals on new areas of research where good practices are lacking or areas where the science has advanced to a point where a report might provide a timely update on evolving standards or provide a framework for understanding and assessing important new approaches that are being applied to HEOR. The [Machine Learning in HEOR Task Force](#) is an example of the latter, and the [Consolidated Health Economic Evaluation Reporting Standards \(CHEERS\) II Task Force](#) is an example of the former.

In some cases, members are informed by the topics that ISPOR—via its councils, conferences, or publications—has indicated are of high importance and timeliness. For example, the Health Science Policy Council Task Force Review Committee looks forward to seeing member-initiated proposals on topics from ISPOR's [Top 10 HEOR Trends](#) and from the upcoming ISPOR Scientific Strategy, to be released in January 2021. Topics are encouraged to address issues that are or will be of enduring interest to multiple stakeholders in the healthcare ecosystem.

The Task Force Review Committee has established criteria for task force proposals and a [proposal format](#) for initiators. The criteria and process for approving new task forces are straightforward. The rationale for the proposal must include a justification including why this good practice guidance is important and its potential impact on the scientific community. The rationale should include the following criteria:

- **Necessity:** Why is this task force required? What are the controversies, issues, or concerns the task force will address?
- **Methodology oriented:** Inherent in ISPOR Good Practices Task Force reports is a focus on methods and approaches to conducting research to inform healthcare decisions and improve health.
- **Relevance to ISPOR's mission and its members:** The task force must be relevant to ISPOR's mission. The report should be of broad interest to ISPOR members and applicable in more than one geographic area.
- **Durability:** The topic of interest should not be a passing trend. It should stand the test of time.
- **Broader applicability:** The task force should not focus on a particular product, technology or program, but rather be applicable to a wide array of technologies, situations, and geographic areas. ISPOR is a global organization.
- **Evidence-based:** The rationale should be supported by empirical studies that resolve or identify underlying uncertainty about research methods. The rationale should also discuss

the implications of using different approaches to study the phenomena, and the expected outcomes from the task force in terms of obtaining consensus or providing recommendations.

If insufficient studies are available to resolve uncertainty for most issues facing the task force, then the emerging task force designation is appropriate.

Proposals should address why a task force is needed, what specific issues it intends to address in the design, conduct, or reporting of outcomes research and/or health economic analyses, and how the task force will support ISPOR's mission.

For more details, see the recently published article, [Criteria and Process for Initiating and Developing an ISPOR Good Practices Task Force Report](#) in the April issue of *Value in Health*.⁴

What's Next?

The practical influence of ISPOR task force reports cannot be understated. ISPOR Good Practices Task Force Reports are among the most highly cited articles in *Value in Health* and have raised the profile of ISPOR as a premier professional organization in the fields of outcomes research and health economics.

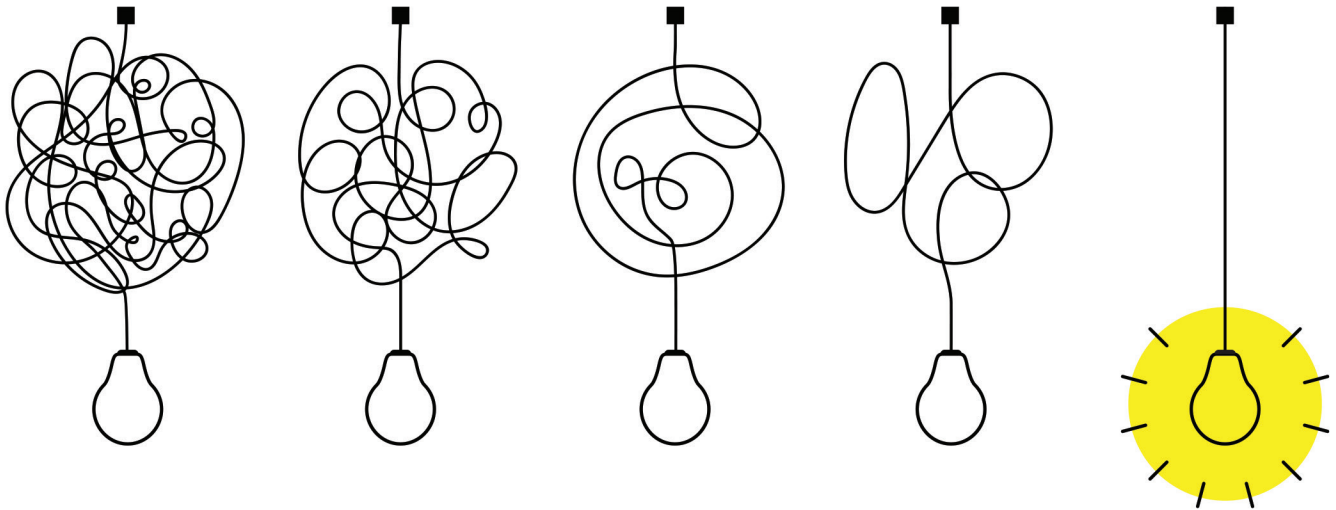
ISPOR staff are available to discuss with any member ideas and proposals for new good practices task forces. They are happy to brainstorm with you and help shepherd you through the process. Send an email to taskforce@ispor.org for more information. •

References

1. Berger ML, Sox H, Willke RJ, et al. Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. *Value Health*. 2017;20(8):1003-1008.
2. US Food & Drug Administration. Framework for FDA's real-world evidence program. Published December 2018. <https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence>. Accessed Jan 29, 2020.
3. US Food & Drug Administration. Patient-reported outcome measures: use in medical product development to support labeling claims—guidance for industry. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims>. Published December 2009. Accessed Jan 29, 2020.
4. Malone DC, Ramsey SD, Patrick DL, et al. Criteria and Process for Initiating and Developing an ISPOR Good Practices Task Force Report. *Value Health*. 2020;23(4):409-415.

¹ In addition, any interested ISPOR member can volunteer as a task force report reviewer. Please visit the task force homepage at <https://www.ispor.org/member-groups/task-forces> to sign up.

² The real-world evidence collaborative was actually a Special Task Force. Special Task Forces are formed to address time-sensitive, policy-related issues. They are subject to different criteria and a different Health Science Policy Council review process.



Getting to simple is no easy task.

Synthesizing complex economic models, methods, and real-world data for healthcare decision makers is what ISPOR's HEOR news magazine does best.



Value & Outcomes Spotlight is an ideal venue for publishing concise reports on methodologies and health policies that demonstrate the value of health economics and outcomes research to a diverse audience of healthcare decision makers. The Editors of *Value & Outcomes Spotlight* invite you to submit your research on topics for upcoming editorial themes:

- Innovative pricing models
- Behavioral economics
- The current state of real-world evidence
- Women and minorities in leadership roles in science and HEOR fields
- The effect of Brexit on health technology assessment
- The economic impact of COVID-19

For more information about submitting your research to *Value & Outcomes Spotlight*, visit ispor.org/vos_authors



ISPOR

Improving healthcare decisions

ISPOR-The professional society for health economics and outcomes research
505 Lawrence Square Blvd, South
Lawrenceville, NJ 08648 USA
www.ispor.org