MARCH/APRIL 2020 VOL. 6, NO. 2

VALUE & OUTCOMES SPOTLIGHT

A magazine for the global HEOR community.

COVID-19: A GLOBAL CRISIS

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MARCH/APRIL 2020
VOL. 6, NO. 2

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

ISPOR
Improving healthcare decisions

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FROM THE EDITOR

Our whole world has been turned upside down by the novel coronavirus, SARS-CoV-2, and the exponential increases in cases and fatalities attributable to COVID-19, the disease to which it gives rise. No person, family, community, or country is immune, and at the time of writing, it is clear that things will get far worse before they will even begin to get better—for most countries, there is currently no light at the end of the tunnel.

Although the economic impact of the COVID-19 pandemic promises to be immense, many of us in the ISPOR community are fortunate enough to be able to maintain our current employment and carry out our business relationships virtually, interacting with one another via videoconferencing technologies and exchanging work products through email. In this regard, we should consider ourselves lucky. But it's a decidedly unlucky situation for those of us who were looking forward to convening this May in Orlando, Florida for ISPOR 2020, which of course has been cancelled. All of us will have to do our best to make "Virtual ISPOR 2020" a productive and fruitful online event.

Value & Outcomes Spotlight prides itself on being agile in the face of rapidly changing circumstances and we have put that into practice in the current issue. Our planned theme is the state of health technology assessment (HTA), and we have the usual feature article providing a global overview of HTA practices, with an accompanying By the Numbers piece highlighting some interesting comparative statistics across countries. We also have a variety of HEOR articles of interest, encompassing such topics as statistical handling of missing data in outcomes research, methods for addressing treatment switching in comparative effectiveness research, and the use of patient-reported outcomes to give voice to the patient perspective in HTA.

In addition to all that, we have scrambled to assemble a wide range of content specific to COVID-19. This begins with an insightful essay by ISPOR President Nancy Devlin, PhD culminating in a call to action for those of us in the HEOR community to respond to this global crisis. We also have a first-person perspective from Siying Zou, PhD, who lives and works in the United States but grew up in Wuhan, China, where the virus originated. She shares the anguish of hearing the news of her mother becoming ill with COVID-19 and details the difficult patient journey that has affected her entire family. Finally, our Q&A section includes 2 interviews of interest, one with Christian Lindmeier, a spokesperson for the World Health Organization (WHO), and the other with Mirjam Kretzschmar, PhD, an infectious disease modeler with the University Medical Centre Utrecht in The Netherlands and a member of the ISPOR Modeling Task Force.

All of us at *Value & Outcomes Spotlight* encourage you to stay safe, continue to practice social distancing, and look to provide help where help is needed as we "pull together by staying apart" during these difficult times.

Sincerely,

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

FROM THE PRESIDENT

COVID-19—A Call to Action for Health Economics and Outcomes Researchers

Nancy J. Devlin, PhD, ISPOR President (2019-2020), Centre for Health Policy, University of Melbourne, Melbourne, Australia

I am writing this from New Zealand, where a state of emergency has been declared and I am experiencing my second week of lockdown. You will no doubt also be adapting to the new personal, family, social, and work circumstances in which we find ourselves. Having succeeded in the first challenge—figuring out good ways to work from home—the new challenge is how to cope with uncertainty about how long the pandemic will remain at crisis levels, and what the implications will be for our work and our families.

> Economic damage from lockdown measures will not be equally distributed—it is likely the misery from this will fall disproportionately on the poor and those in secondary labor markets, including "gig economy" workers, who are pushed into poverty.

I am amazed by the spirit and resilience of my colleagues in Australia and around the world. And I am full of admiration for colleagues with young children; with childcare and schools closed, they somehow continue to work, appearing on videoconferences with partners and children in the background, all vying for use of laptops and work spaces.

I did not imagine when I began my term as ISPOR President that one of the decisions the Board of Directors would have to make this year was cancelling the ISPOR 2020 conference in Orlando (the first time in ISPOR's 25-year existence that it has cancelled a major event). This was not a decision taken lightly, and considerable effort went into assessing the implications. But ultimately there was no option: ISPOR is committed to global health and we take seriously our duty of care for the health and well-being of our members and stakeholders.

Beyond changing our immediate personal and working circumstances, the COVID-19 pandemic will (and should) lead us to radically rethink our world. It has revealed failures in political leadership. It has highlighted major weaknesses in public health and healthcare systems. It has brought to the fore fundamental questions about the trade-offs society is prepared to make between population health and economic activity, while also reminding us about the interconnectedness between health and wealth. There are also questions about behavioral responses to the crisis and how to strike the right balance between encouraging and compelling individuals to behave in a manner consistent with collective interests.

ISPOR is the leading international body for health economics and outcomes research (HEOR). As a community of 20,000+ HEOR professionals worldwide, we have a responsibility to consider the implications of the pandemic for our HEOR scientific priorities. We need to ensure HEOR evidence informs healthcare delivery and policy in and following the pandemic—the lessons that we can learn from this will be invaluable in planning for future, potentially much more fatal, crises.

Identifying HEOR scientific priorities for COVID-19 research

Which ethics committee signed off approval for this worldwide study into comparative public healthcare systems?

—Professor Jo Wolff, Oxford University, United Kingdom

COVID-19 and the responses to it by government, healthcare systems, businesses, and individuals generate important questions that HEOR can help to address.

The governments of the world have taken very different strategies in reacting to and managing the pandemic, creating a kind of wholesale natural experiment about restrictions on travel, gatherings, continuation of businesses and schools, and self-isolation or quarantine.

Governments have had to make rapid-fire judgments about the willingness to sustain economic harm to contain the health of people, in the presence of considerable uncertainty as to the effectiveness of those strategies, the period of time for which they will be required to be in place in order to sustain that effectiveness, and their real societal cost. Evaluation to understand the differences in effects and costs of these measures will be difficult but essential to inform economic and health policy in the post–COVID-19 world. Yet these evaluations pose methodological challenges: the options are huge in scale and far from "marginal" changes; the perspective from which to evaluate them necessarily extends beyond the narrow "healthcare perspective"; and what decision rule do we use to judge value for money in such a context?

The availability of data is a limiting factor in undertaking research at present. Differences in the availability and use

of testing confounds the interpretation of and comparisons between rates of infection in the populations of different countries, and the rates of mortality among those infected. In some countries, testing and tracing was maximized; in other countries, access to testing was severely restricted, further complicating an understanding of transmission, prevalence of illness, and the relative effectiveness of strategies to limit these. What was the optimal strategy? And how much avoidable harm did the world's nations' deviations from that cause?

> COVID-19 and the responses to it by government, healthcare systems, businesses, and individuals generate important questions that HEOR can help to address.

Economic damage from lockdown measures will not be equally distributed—it is likely the misery from this will fall disproportionately on the poor and those in secondary labor markets, including "gig economy" workers, who are pushed into poverty. Given what we know about the socioeconomic determinants of health, the *health* consequences of these economic measures will therefore also be unequally distributed—and will have implications for health well beyond the immediate crisis. We need evidence on that, so effective policy measures can be targeted.

Meanwhile, what is happening to supply, demand, and access to other health services during the pandemic in the world's healthcare systems? What health needs and healthcare utilization have been deferred, and what will be the consequences of that in the post-COVID world? How have morbidity and mortality from non-COVID infectious diseases (and from noninfectious causes) been affected by isolation and lockdowns? Presumably some will have been avoided altogether (eg, car crash fatalities), and some may worsen (eg, domestic abuse fatalities and injuries, alcoholism), while other health problems will be "stored up" (eg, mental health problems, cancers), and future outcomes will be worse, due to delayed diagnosis and missed treatment opportunities.

What are the implications for the health and quality of life of those for whom this period of enforced isolation has disrupted the delivery of essential services, such as those with mental health problems and those with disabilities? What are the effects of isolation and lockdown on the quality of life of those without pre-existing mental health problems, but who are now struggling with anxiety, depression, and uncertainty? How has the lockdown affected vulnerable populations, including elderly people in residential care?

How are prioritization decisions being made when demand exceeds capacity in healthcare systems during the peaks of the COVID-19 crisis—particularly in systems where "rationing" has not previously been accepted? Who is making these decisions—are they being made consistently—and on what basis? Who is benefiting and what is being sacrificed?

The pandemic has also revealed different levels of preparedness among healthcare systems: lack of personal protective equipment (PPE) for frontline staff may itself have led to a considerable avoidable burden of ill health. What are the cost and benefits of improved PPE? What are the supply or other constraints that have led to PPE not being available for frontline clinical staff during COVID-19? More broadly, what is the appropriate balance between spare capacity and technical efficiency in healthcare provision?

This is far from an exhaustive account of the kinds of questions HEOR could usefully address. ISPOR now has a new and important role to facilitate us working together collectively as an HEOR community to establish the research priorities. And each of us, as ISPOR members, should consider how to pivot our research agendas, to use our skills to address the new and emerging research needs.

ISPOR's role

As I write, ISPOR is working hard to develop its first online conference program to take the place of the in-person event in Orlando. In addition to the plenaries and panel sessions which had already been planned, we will add an online preconference session where HEOR aspects of the COVID-19 situation and their implications for future research priorities will be discussed. **I encourage all ISPOR members to log in, tune in, and engage. We welcome your ideas about how ISPOR can help to mobilize HEOR efforts now and over the coming year to produce better data, better evidence, and real solutions.** It is important we learn as much as we can from this crisis—and the enormous human and economic cost that has and is still to be incurred—to better prepare us for the future.

At the start of the year, ISPOR embarked on an important new project to establish HEOR research priorities. That project has made excellent progress and is well positioned to incorporate new research topics relating to COVID-19. ISPOR leaders will meet in the coming months to establish ISPOR's HEOR science priorities for the next 5 years, informed by results of that work.

ISPOR and its member groups will organize special webinars and discussions around COVID-19 and will continue to support its members with the latest information on this rapidly changing situation. ISPOR is committed to its mission and to serving its members and the broader healthcare audience during the extraordinary global healthcare crisis that COVID-19 presents. The field of HEOR has never been more important.

Wherever you are, I hope you, your family, and your community stay safe and stay well. Be kind to each other.

ISPOR SPEAKS

Dialogue With Decision Makers: Collaborating With Payers to Advance Health Economics and Outcomes Research

Nadia Naaman, Senior Director Scientific & Health Policy Initiatives, ISPOR

A few decades ago when ISPOR was founded, our members represented mostly healthcare researchers and academicians. But over the years, slowly but surely, our membership experienced a steady expansion of different stakeholder groups, such as regulators and assessors, payers and decision makers, the life sciences industry, healthcare providers, and of course, patient engagement organizations.

ISPOR believes that every healthcare decision should be informed by the best scientific research derived from rigorous, proven methodologies. We also believe that the research should be used and applied by all healthcare stakeholders. As a way to address these needs, ISPOR has established several councils to represent these different stakeholders and has provided a platform where each of these stakeholders can interact and engage in discussions on key issues.

One of the stakeholder groups that ISPOR has dedicated a lot of effort and resources to cultivate and collaborate with are healthcare decision makers, especially those responsible for reimbursement policies for pharmaceuticals and other health technologies, as these are the core people who play an integral role in the healthcare system. These decision makers are responsible for determining which health technologies are reimbursed, and this key group may or may not have the ability to influence the final price of the product or service. In short, this group is collectively referred to as "payers" and represents the public and private organizations who ultimately decide whether a health technology is reimbursed and at what price.

The *ISPOR Book of Terms* defines a "healthcare payer" as *the party responsible for the financing and payment of healthcare for a population of eligible persons.* Due to the heterogeneity of health systems throughout the world, the types of payers vary across countries and within countries. Payers can be government bodies at the national and/or regional/local levels, private/statutory insurers (both for-profit and nonprofit), and self-funding employers.

As a multistakeholder organization dedicated to improving healthcare decisions, ISPOR recognizes that payers are a critical stakeholder group who can help apply and advance the science of health economics and outcomes research (HEOR). In a strategic effort to start a dialogue and collaborations with these decision makers, ISPOR established a payer engagement initiative to increase ISPOR's interaction with the payer community, to drive awareness about the benefits of HEOR in healthcare decisions, and to ultimately establish ISPOR as a key resource and trusted partner for healthcare payers around the world.

Since 2007, ISPOR has hosted an annual Health Technology Assessment (HTA) Roundtable, which has grown to cover the 5 major regions of the world. Roundtable attendees include representatives from public HTA bodies, public and private payers, decision makers, and government-contracted academic centers (if no HTA body exists in the country). In North America, the active and candid participation of payers has been the key to the high level of interest and sustained overall success of these roundtable events.

ISPOR has many resources that are relevant to payers; however, few payer organizations are using these resources in a systematic way. Recognizing the importance of this key stakeholder group, many ISPOR members have asked to have more payers participate at ISPOR conferences, as much of the research that has been conducted in the HEOR field must be accepted and applied by them.

This year, ISPOR is excited to introduce new opportunities to promote the dialogue with decision makers that focus on the payer perspective. Our goal is to create a series of events and programs that bring together ISPOR's multistakeholder audience and provide unique opportunities to interact and collaborate with this influential payer group. With the continued development of high-cost therapies, payers and manufacturers are increasingly engaging in performance-based managed entry agreements. The collaborative nature of these payment schemes require all parties to work in alignment. To ensure the success of these arrangements there is a need to agree on the information provided by manufacturers at the time of launch, and the proper processes to collect and analyze real-world data post-launch. As a multistakeholder organization devoted to improving healthcare decisions, ISPOR is well-suited to further this discussion and come closer to finding solutions.

Healthcare decision making is increasingly complex, and the best way to find solutions is to work across stakeholder types toward a shared outcome. ISPOR is dedicated to providing an unbiased, collaborative environment for interactive dialogue that includes all perspectives across the healthcare continuum. We look forward to continuing to lead the way in improving decision making in health for today, tomorrow, and well into the future.

HEOR NEWS

1 Potential Costs of Coronavirus Treatment for People With Employer Coverage (Petersen-KFF Health System Tracker)

As the new coronavirus spreads within the United States, questions have arisen over the potential costs people may face if they become severely ill and need treatment. To address concerns over costs associated with the COVID-19 virus, Vice President Mike Pence met with a group of large private insurers, who agreed to waive copayments and deductibles for COVID-19 tests. However, America's health insurance plans clarified that the out-of-pocket costs for treatment (such as hospitalizations for more serious cases) would not be waived, meaning people with private insurance who face deductibles could be on the hook for large costs.

https://www.healthsystemtracker.org/brief/potential-costs-of-coronavirus-treatment-for-people-with-employer-coverage/

2 4 Ways Government Can Use AI to Track Coronavirus (GCN)

Government health agencies can leverage artificial intelligence (AI) technology to limit the spread of the new COVID-19 virus and other diseases in 4 ways: prediction, detection, response, and recovery.

https://gcn.com/articles/2020/03/10/ai-coronavirus-tracking.aspx

3 ICER Indefinitely Postpones Public Meetings for Sickle Cell Disease and Cystic Fibrosis, Expands Other Assessment Timelines Up to 3 Months (ICER)

Like many other national and international healthcare organizations holding regular meetings, the Institute for Clinical and Economic Review (ICER) has postponed some of its meetings and expanded the timeline on other assessments because of the COVID-19 pandemic. "We are hopeful these expanded timeframes will enable all stakeholders to instead focus on meeting the needs of their patient communities during this national emergency."

https://icer-review.org/announcements/covid19_hiatus/

4 Medicare For All: If Not Now, When? (Health Affairs Blog)

While some pundits say the strong push by Democrats for Medicare for All may succumb to political realities, Adam Gaffney argues that while the hurdles are formidable, "steep political odds hardly compel us to abandon Medicare for All." He says history suggests that movements organized around ambitious demands can over time create the conditions for their passage, and that demands for radical change often advance, rather than undermine, the prospects for more incremental progress in the interim.

https://www.healthaffairs.org/do/10.1377/hblog20200309.156440/full/?utm_campaign=Industry+news+&utm_content=twitter&utm_medium=social&utm_source=twitter

5 Does Pharma's Future Lie in China? (pharmaphorum .com)

Nooman Haque, managing director, Life Sciences, Silicon Valley Bank UK, says if the pharmaceutical industry wants to continue capitalizing on the power of collaboration, it needs to open doors to cross-border investment. "Primarily, we believe the future lies in a partnership with China," Haque says. "The East and West have their own very different healthcare challenges, but it is precisely these differences that present us with a unique opportunity for cross-border collaboration."

https://pharmaphorum.com/r-d/views-analysis-r-d/does-pharmas-future-lie-in-china/?utm_campaign=Industry+news+&utm_content=twitter&utm_medium=social&utm_source=twitter

6 Estimating the Unit Costs of Healthcare Service Delivery in India: Addressing Information Gaps for Price Setting and Health Technology Assessment (Applied Health Economics and Health Policy)

India's flagship National Health insurance program (AB-PMJAY) requires accurate cost information for evidence-based decision making, strategic purchasing of health services, and setting reimbursement rates. To address the challenge of limited health service cost data, this study used econometric methods to identify determinants of cost and estimate unit costs for each Indian state.

https://link.springer.com/article/10.1007%2Fs40258-020-00566-9

7 Shared Decision Making: From Decision Science to Data Science (Medical Decision Making)

According to this study's authors, while accurate diagnosis of patients' preferences is central to shared decision making, often missing from clinical practice is an approach that links pretreatment preferences and patient-reported outcomes. The authors (Azza Shaoib, Brian Neelon, and Leslie A. Lenert) propose a Bayesian collaborative filtering algorithm that combines pretreatment preferences and patient-reported outcomes to provide treatment recommendations.

https://journals.sagepub.com/doi/10.1177/0272989X20903267

8 Model-Assisted Cohort Selection With Bias Analysis for Generating Large-Scale Cohorts From the EHR for Oncology Research (Flatiron Health)

To efficiently build research cohorts of greater scale without sacrificing quality, a team of data scientists, software engineers, and clinicians at Flatiron Health have developed a technique that combines machine learning and natural language processing with human review called Model-Assisted Cohort Selection with Bias Analysis to analyze the data found in unstructured documents, such as clinician notes and pathology reports, in electronic health records (EHRs).

https://rwe.flatiron.com/machine-learning-bias-analysis-real-world-data

9 The Interaction Between Price Negotiations and Heterogeneity: Implications for Economic Evaluations (Medical Decision Making)

Although economic evaluation is an important element of the decision-making process for the reimbursement of drugs, and heterogeneity can be considered an explained variation in clinical or economic outcomes based on the clinical and sociodemographic characteristics of patients, this study's authors say to their knowledge, the relationship between price negotiations and population heterogeneity has not been considered in the literature to date.

https://journals.sagepub.com/doi/10.1177/0272989X19900179

10 Competitive Physician Prices in Fee-for-Service Medicare (Health Affairs Blog)

Experts have criticized the administrative approach to setting traditional Medicare prices since its inception. But trying to set up a more competitive pricing system faces several challenges, as outlined by Bryan Dowd, Roger Feldman, and Robert Coulam: (1) the degree to which services are "shoppable" by beneficiaries; (2) provider consolidation, which reduces the number of bidders and imparts pricing power to the remaining providers; and (3) the inherent reluctance of consumers to change providers, which can make the market less price competitive.

https://www.healthaffairs.org/do/10.1377/hblog20200312.579807/full/

11 US Government Aims at High Insulin Prices With Plan for $35 Copay in Medicare (Reuters)

The Trump administration in March turned back to its pledge to fight high US drug prices with a plan to limit the out-of-pocket cost for insulin, a life-saving medicine, to $35 per month for many people with diabetes who are enrolled in Medicare.

https://www.reuters.com/article/us-usa-healthcare-insulin/u-s-government-aims-at-high-insulin-prices-with-plan-for-35-copay-in-medicare-idUSKBN20Y1WG

12 Hub Providers Can Be the Source of the Best Real-World Evidence (Pharmaceutical Commerce)

Rational value-based contracts must be based on the ability to track the outcomes or continued health of patients. While most of these data comes from payers' claims records and electronic health records, another source of real-world evidence—and one that could play into a much wider range of value-based contracts—is the pharma industry's hub and patient-support providers, which routinely gather data from patients. "In some cases, they are in touch with them daily, not just for medical data, but scads of data on patients' moods, emotions, and concerns," says Nicholas Basta.

https://pharmaceuticalcommerce.com/opinion/hub-providers-can-be-the-source-of-the-best-real-world-evidence/

RESEARCH ROUNDUP

Section Editor: **George Papadopoulos**, Emerald Corporate Group Pty Ltd, Sydney, Australia

Healthcare decision makers (whether they are payers, regulators, clinicians, or health economists) have to grapple with a variety of evidence presented to them. Interpretation of Kaplan-Meir plots or response rates are but 2 presentations of that evidence, and we have selected 2 recent articles that discuss the presentation and interpretation of these data. Finally, qualitative health-preference research also can be utilized, and we present a paper that discusses a set of guidelines to improve the frequency and quality of reporting.

Proposals on Kaplan–Meier plots in medical research and a survey of stakeholder views: KMunicate

Morris T, Jarvis C, Cragg W, Phillips P, Choodari-Oskooei B, Sydes M. *BMJ Open*. 2019;9(e030215): doi:10.1136/bmjopen-2019-030215

Summary

We all use Kaplan-Meier curves or plots, but how is the information best communicated to both decision makers and non-decision makers? What is the level of uncertainty in the difference estimates in survival time between the treatment groups? In this *BMJ Open* article, Morris, et al present research on improvements that can be made to the presentation of Kaplan-Meier curves to show the status of patients over time, and to illustrate the uncertainty of the estimates. The authors then survey stakeholders in order to understand which improvements are preferred. The authors created 6 improvements of the "standard" Kaplan-Meier plot from 3 published phase III randomized trials, and surveyed 1174 participants over a 6-week period. Most proposals were more popular than the "standard" Kaplan-Meier plot. The most popular proposals were in 2 categories:

1. An extended table beneath the plot depicting the numbers at risk, censored and having experienced an event at periodic timepoints.

2. Confidence intervals around each Kaplan-Meier curve, the latter one a favorite of mine.

Relevance

The presentation of an extended table beneath the plot depicting the numbers at risk (Plot A in Figure 2 of the paper), together with confidence intervals around the estimates (Plot E in Figure 2), would greatly increase the ability of both expert and non-expert decision makers to understand the survival times more easily. Kaplan-Meier plots remain an important tool in research and analysis and the development of a more visually meaningful presentation of the result is a great step forward.

Reporting formative qualitative research to support the development of quantitative preference study protocols and corresponding survey instruments: guidelines for authors and reviewers

Hollin I, Craig B, Coast J, Beusterien K, Vass C, DiSantostefano R, Peay H. *Patient*. Published online: December 2019.

Summary

Hollin, et al have developed a set of guidelines for authors and reviewers to improve the frequency and quality of reporting of quantitative health preference research. The guidelines focus on formative qualitative research used to develop robust and acceptable quantitative study protocols and corresponding survey instruments in health preference research.

The guidelines have 5 components with subcomponents:
1. Introductory material (4 domains)
2. Methods (12)
3. Results/findings (2)
4. Discussion (2)
5. Other (2)

Relevance

Qualitative research is not often published, but the publication of formative qualitative research is a necessary step toward strengthening the foundation of any quantitative study. These guidelines should aid researchers, reviewers, and regulatory agencies, and at the same time, promote the transparency within health preference research.

Response rates and durations of response for biomarker-based cancer drugs in nonrandomized versus randomized trials

Gyawali B, D'Andrea E, Franklin J, Kesselheim A. *J Natl Compr Canc Netw*. 2020;18(1):36-43. doi:10.6004/jnccn.2019.7345

In this original research article, Gyawali, et al evaluated whether the response rates and durations of response of targeted cancer drugs observed in nonrandomized controlled trials (non-RCTs) are consistent when these drugs are tested in randomized controlled trials (RCTs). The authors compared the response rates and median durations of response in non-RCTs versus RCTs using the ratio of response rates and the ratio of durations of response (defined as the response rates [or durations of response] in non-RCTs divided by the response rates [or

durations of response] in RCTs). The ratio of response rates or durations of response was pooled across the trial pairs using random-effects meta-analysis. Both non-RCTs and RCTs were available for 19 drug-indication pairs selected. The response rates and durations of response in non-RCTs were greater than those in RCTs in 63% and 87% of cases, respectively. The pooled ratio of response rates was 1.06 (95% CI, 0.95–1.20), and the pooled ratio of durations of response was 1.17 (95% CI, 1.03–

1.33). Response rates and durations of response derived from non-RCTs were also poor surrogates for overall survival derived from RCTs.

Relevance

As more and more drugs, especially new targeted cancer drugs, are slated to receive regulatory approval globally, based on durable responses in non-RCTs, this is important research to consider. A critical eye should be cast over the use of durable responses data derived from non-RCTs, because the responses could be overestimates and poor predictors of survival benefit. The authors conclude that caution must be exercised when approving or prescribing targeted drugs based on data on durable responses derived from non-RCTs.

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

ISPOR—The Professional Society for Health Economics and Outcomes Research

ISPOR 2020 Conferences

Virtual ISPOR 2020
May 18-20

HEOR: Advancing Evidence to Action

May 14: New Plenary Session *"HEOR in the Era of COVID-19"*
May 18-20: Virtual Conference

ISPOR-FDA Summit 2020

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

Summit Postponed
Visit the website for updates

12-15 September
Seoul, South Korea

Next Generation Healthcare in Asia Pacific: Where Technology Meets Patients to Improve Care

Abstract Notifications: 10 June
Early Registration Deadline: 28 July

14-18 November | Milan, Italy

Improving Health: Establishing Incentives and Sharing Value

Early Registration Deadline: 6 October
Abstract Submissions Open Through 8 July

Looking ahead to 2021 Conferences:

ISPOR 2021
May 15-19
Montreal, Canada

ISPOR Latin America 2021
Mexico City, Mexico

ISPOR Europe 2021
6-10 November
Paris, France

ISPOR
www.ispor.org

The Society's Annual Conference Is Now a Virtual Event

SAVE THE DATE

Virtual ISPOR 2020

MAY 18-20

HEOR: Advancing Evidence to Action

The 3-day virtual conference will include issue panels, workshops, podium presentations and symposia, as well as 3 featured plenary sessions:

- Health Policy—Designing for the Future
- HEOR and Clinical Decision Making—Advancing Meaningful Progress
- On the Road to Enhanced Cost-Effectiveness Analysis—New Directions, New Milestones

NEW **A virtual plenary session, *HEOR in the Era of COVID-19*, scheduled for May 14 10:00AM-12:00PM EDT, will be offered free to members and non-members.**

The Virtual Short Course Program will be available beginning in June. Visit the ISPOR website for dates and times.

Detailed program information and registration will be announced soon. Visit www.ispor.org/ISPOR2020 for updates.

FROM THE JOURNALS

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

Value in Health. 2020; 23(2):200–208.

Optimal Design of Population-Level Financial Incentives of Influenza Vaccination for the Elderly

Mu Yue, Yi Wang, PhD, Chng Kiat Low, Joanne Su-yin Yoong, Alex R. Cook

Influenza (or the flu) is caused by 3 types of influenza virus. It is a rapidly evolving virus, causing 3 to 5 million severe cases per year and approximately 260,000 to 560,000 deaths per year.[1] The case fatality is highest among high-risk patients (ie, children, the elderly, and people with other comorbidities). It is a seasonal disease mostly occurring in the winter but can happen any time along the equator. Flu vaccines are developed twice a year to match the predicted mix of types of viruses for the coming season. Vaccination is recommended annually for the high-risk groups, but several countries recommend it to everyone. There are some countries where it is offered free of charge (United Kingdom), or at a relatively low cost.[1] However, uptake of the flu vaccination is variable.

In the United Kingdom, where a universal vaccine program for school children was introduced in 2013, a retrospective observational study of 500 primary care practices (~700,000 children) showed an increase in vaccination uptake from 2012–2013 to 2013–2014 in targeted children aged 2 to 3 years, both in children with a high-risk medical conditions (from 40.7% to 61.1%) and those without (from 1.0% to 43.0%).[2] According to the United Kingdom's official statistics on seasonal flu vaccines, the uptake among individuals over 65 years of age was 71.3% in 2018, and among those at high risk, 46.9%.[3] In Singapore (Yue et al),[4] the current uptake of the flu vaccine is around 15% among school children and 17% among the elderly, despite recommendations for vaccination from the local ministry of health. We review the article by Yue et al studying the impact of a financial incentives among the elderly in Singapore.

The authors invited 4000 individuals, who all participated in a population-based health study and indicated they would be available for future studies. Participants were randomized into 4 groups. People in Group 1 received a survey regarding their thoughts about the flu vaccine (which was to be completed in 2 months), and a SGD $10 (US $6.90) shopping voucher (this served as the control group). In the 3 intervention groups, people were asked to fill in the survey and also to go for the vaccine (at their own cost, at SGD $32 [US$22.08]), in return for a small compensation of SGD $10, $20, or $30 (US $6.90, $13.80, and $20.69) in the form of shopping vouchers. The outcome measured was "participation within 2 months," corresponding to returning the survey in Group 1 and returning both the survey and vaccination certificate dated within the study period. Letters returned from unknown addresses and those vaccinated within the previous 6 months were excluded from the denominator for calculating the participation.

Overall response was 9.3%, with highest in Group 1 (16.9%) and extremely low values in the 3 other groups (4.5%, 7.5, and 9.2%, respectively). Nevertheless, the increase in the total incentive from SGD $10 to $20 (US $6.90, $13.80) in shopping voucher value was statistically significant; further increase was not. However, in terms of trends, both males and females were more likely to participate if SGD $30 (US $20.69) was offered versus SGD $10 (US $6.90), while some other demographic factors mattered: Chinese elderly were more sensitive to incentives, as well as the nonworking elderly, and those over 75 years responded much more strongly to the incentives. The authors looked for the "optimal" financial incentive but considered the vaccine uptake as an external variable. Therefore, this is not a true optimization along multiple parameters. Their key finding is that considering transmission dynamics, an incentive between SGD $10 and $20 (US $6.90 and $13.90) minimizes the cost per completed vaccination from a health system perspective.

In terms of the survey results, of those who responded, vaccinations that took place in a general practitioner's office or polyclinic were preferred by 85% of respondents; few preferred vaccinations in their own home or other options. Importantly, 76% perceived the vaccine as safe, but few people considered themselves being at risk of infection without the vaccine (35%).

Circumstances related to the flu vaccine are unique in Singapore in many ways: there is less seasonality due to its equatorial location, the funding of healthcare is based on medical savings account, and it is a developed yet small country. However, the topic of the paper is very important, especially considering the current COVID-19 virus pandemic. Flu is a potentially deadly disease among high-risk groups and that can put additional strain on the health system given the presence of COVID-19. Although a vaccine is available for the flu, the awareness of the severity of the disease and the uptake of the vaccine are very low. Direct financial incentives may have an important role in targeting the high-risk groups. However, more ideas will be needed to substantially increase the number of patients showing up for their annual flu shots.

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FROM THE REGION

ISPOR's Health Technology Assessment and Patient Representative Roundtables: Strengthening Patient-Centered Decision Making in Asia Pacific and Globally

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Against the backdrop of rapid institutional reforms and development for national health technology assessment (HTA) in China, ISPOR hosted HTA and Patient Representatives Roundtable discussions in Beijing, China on 25 October 2019. ISPOR's HTA and Patient Representative Roundtables are platforms to advance scientific methods, facilitate information sharing about the development of HTA, and strengthen the role HTA plays in optimizing healthcare decisions. These roundtables are ideal opportunities for ISPOR to bridge the gap between technology assessors, private and public payers, regulators, and patients, and the discussions focus on innovative ways to improve health globally and make healthcare decision making more patient-centric. ISPOR HTA and Patient Representatives Roundtables are convened regularly in Asia Pacific, Europe, Latin America, Middle East and Africa, and North America.[1,2]

The ISPOR Asia-Pacific HTA and Patient Representatives Roundtables enjoyed broad representation from key experts and decision-making bodies from the region, including the Pharmaceutical Benefits Advisory Committee (Australia); Health Technology Assessment in India (India); HTA Committee (Indonesia); Health Insurance Review & Assessment Service and National Evidence-based Healthcare Collaborating Agency (South Korea); Center for Drug Evaluation (Taiwan); National Institute of Public Health and National Institute of Social Security and Population Research (Japan); Health Technology Assessment Section, Ministry of Health, Malaysia; Philippine Health Insurance Corporation (Philippines); Agency for Care Effectiveness (Singapore); Health Intervention and Technology Assessment Program (Thailand); and HTA department (Mongolia). Patient organizations that were represented included the Heart to Heart Foundation (Thailand), Lymphoma Association of China, China Organization for Rare Diseases, Philippine Alliance of Patient Organizations, Vietnam Hemophilia Group, China Rare Disease Organizations Development Network (Mainland China), and the Psoriasis Association Taiwan.

> A major thread of discussion centered around ways payers are bringing access of high-cost innovative therapies to patients while still maintaining acceptable budgets.

The key topics of the roundtables centered on managing high-cost therapies and patient participation in HTA and healthcare decision making. Participants presented specific cases of managed entry schemes, negotiation mechanisms and approaches for pricing and reimbursement, HTA harmonization across the globe, HTA in universal health coverage implementation, and patient involvement in healthcare decisions.

Improving Patient Access to Innovative Technologies

A major thread of discussion centered around ways payers are bringing access of high-cost innovative therapies to patients while still maintaining acceptable budgets. Jurisdictions are taking highly varied approaches to this issue, ranging from direct centralized negotiation in China to outcomes-based arrangements in Australia and South Korea. Chinese payers have leveraged their purchasing power and large market to extract steep price cuts for many orphan drugs and have also sped up review and approval processes significantly. The Chinese government is also conducting more frequent comprehensive reviews and updates of the national reimbursement drug list, with the latest update occurring in 2019. Currently, all new therapies under consideration are required to undergo review in the areas of clinical efficacy, pricing benchmarks, budget impact analysis, and health economics (budget impact analysis and health economic analysis were optional previously). Additionally, the government is also engaging in a program of high-volume centralized purchasing of generics through their "4+7 Plan," which has led to lower prices for a wide variety of medicines.[3] While such approaches have yielded rapid and dynamic results, how these changes will affect the healthcare system in terms of systematic and transparent processes toward value and efficacy assessment, prioritization and access, and health technology innovation remains to be seen.

Risk-sharing agreements or other managed-access programs have been in practice in South Korea and Australia for several years and have provided incentives and pathways for the adoption of promising new technologies for vulnerable patients where limited data may exist. While there have been some examples of success with these programs, significant challenges remain, particularly regarding capacity and bandwidth of payers in collecting data and assessing the relevant evidence. And since many of these arrangements are only active for 4 to 5 years per contract, the questions surrounding long-term efficacy and value are harder to answer. Many studies that utilize narrow time horizons or surrogate endpoints for the candidate interventions are said not to adequately capture the full costs and value that are expected to be realized throughout the technology's life cycle. Additionally, the arrangements themselves can bring substantial risk and uncertainty.

Thus, some payers still feel hesitant to pursue these types of arrangements (except in very special cases). It was expressed by many participants that to make such arrangements more feasible in the region, additional work needs to be done by innovators to generate acceptable evidence for payers to mitigate uncertainty and risk wherever possible. For example, there should be enough of an initial correlation within the clinical trials and a sufficiently robust accompanying body of outcomes data to support effective decision making.[4] Payers should also have a better understanding of the potential market impact of reimbursement and renegotiation decisions, which could affect the availability of certain products in their countries.

According to one prominent patient advocate in the region, data are an important tool for patient organizations to present their case to decision makers, and that without data, a patient is just another person with an opinion.

Patient Involvement in HTA in Asia Pacific: Where Are We?

As patients and patient advocates are becoming empowered to take ownership of their healthcare, they are increasingly laying pressure on HTA bodies and policy makers and emphasizing the importance of their involvement in informing policy and HTA decisions. At the same time, there is rising consensus in the region among policymakers that healthcare decision making and delivery should be patient-centric and equitable. Many jurisdictions in the region have already formally incorporated patient involvement in their HTA processes. In Taiwan, 2 patient representatives are invited to participate in the Pharmaceutical Benefit and Reimbursement Standard joint meeting as nonvoting members. In Australia, the Pharmaceutical Benefits Advisory Committee has 2 expert consumer (patient) representatives, and schedules consumer hearings to facilitate dialogue. Australia also established the HTA Consumer Consultative Committee in 2017 that provides strategic advice and support to the principal Health Technology Assessment Committees and the Department of Health with the inclusion of consumer representatives. While these examples are encouraging, there are still questions among patients as to whether this is enough, as these representatives do not have voting power in some jurisdictions and may have a limited capacity in providing input. Patient groups also question whether such a small patient delegation on these committees could be truly representative of the broader community, even if they may be expertly qualified. And for groups that still lack formal participation mechanisms in their respective jurisdictions or feel that such processes are lacking, advocacy remains their primary recourse, which has its own limitations. While progress is occurring, much more needs to be done to ensure that these processes are achieving the ultimate objective of making decisions patient-centric. To that end, key questions have emerged, namely: (1) What is the proper role of patients in HTA and healthcare decision making? (2) Where should patients get involved in the process? and (3) What can patients meaningfully contribute to the process?

Managing Uncertainty: Local Data Constraints and Future Investment

Many jurisdictions in Asia Pacific struggle with a paucity of local population data, which means that many important reimbursement decisions must be taken based on potentially limited relevant evidence. Challenges remain in making data and evidence available and adaptable for local considerations. China is taking large strides toward incorporating and utilizing big data in healthcare decision making at all levels, with the establishment of a China Real World Data and Studies Alliance (ChinaREAL) and investment in data infrastructures.[5] The ChinaREAL collaboration has resulted in the production of technical guidance documents including databases and registries for research purposes, epidemiological and statistical considerations in the assessment of treatment effects, and key methodological issues in pragmatic randomized controlled trials. Regionally, however, there are questions surrounding managing uncertainty, including what structure and resources are needed to clarify the impact and relevance of data. Specifically, how do we collectively define an intervention's level of impact or magnitude of benefit? Is it just high unmet need being met? What is a significant clinical benefit—is it defined in terms of breadth or depth? How do patients value judgments differ from society as a whole? And the question of changing priorities and realities in the light of evolving evidence and perspectives necessitates clarity of approaches surrounding disinvestment and de-listing of technologies.

What Can Patients Contribute?

Based on the notable efforts many patient organizations are making in the region, it was clear that patient data are one of the most powerful witnesses they can provide. According to one prominent patient advocate in the region, data are an important tool for patient organizations to present their case to decision makers, and that without data, a patient is just another person with an opinion. Patient representative organizations have taken incredible efforts to generate patient-centric data for decision makers, as well as publishing reports and presenting to policymakers to emphasize the special considerations that HTA needs to make for rare diseases. Patient-generated data can provide insights into patient preferences and priorities for policymakers, and patient inputs can help researchers to better capture the burden of disease and cost of illness. Jurisdictions in the Asia Pacific region have incorporated various mechanisms for capturing patient data and perspectives. For example, Taiwan has fielded a patient questionnaire with an online submission form and guidelines to generate patient feedback; Australia also utilized a similar feedback process. Nonetheless, quality of feedback and patient data remains a challenge, as there is no formal system for assessing validity or considering conflicts of interest (lobbying influences) in Australia.

A key challenge for the future will be making patient inputs and data more meaningful for payers and impactful in

health policy. The first part of this relates to the ability of patient organizations to effectively leverage their voice and position as a credible and vital stakeholder in the process. To lend more weight to their voices, "expert patients" are needed—both globally and regionally—to strengthen the foundation for organizational/institutional participation and incorporation of perspectives, and education will remain a critical part of this. Patients should also be better advocates (not just for their specific diseases but for their stakeholder group as a whole), as they will be more effective in a unified way. A "turfing" mentality still exists among some patient societies as they vie for influence and limited resources.

The other part of this relates to the quality of patient data. For policymakers the question becomes: What kind of data are really helpful for decision making? With respect to qualitative data, decision makers count specific and rich patient testimonials (ones that share patients' personal disease experience and effects on the quality of their lives) as most useful to them. From a research standpoint, patient perspectives have the potential to ensure that clinical trial and observational study designs have assumptions, objectives and endpoints that are better aligned with the real world to optimize outcomes.[6]

Conclusions

For HTA to be successful, it should be timely, relevant and practically usable for decision makers, and follow an inclusive and transparent process that proactively emphasizes local horizon scanning and priority setting. Patients are a key stakeholder group for healthcare and should be actively involved in HTA, but where and how they are involved in the process needs to be clarified further. Moreover, there is an important role for patients to play in clinical trial design and in the design and interpretation of observational studies.

Development and utilization of local data will be an essential priority for Asia Pacific countries in the immediate term to mitigate global data reliance. Patient-reported outcomes data are also set to play a more prominent role in future evidence considerations, including in China. Further works needs to be done to strengthen health infrastructures and to bridge evidence gaps globally through health economics and outcomes research. Finally, it will be essential for HTA stakeholders to more actively facilitate translation of their recommendations into policy. A model for this could be Malaysia, which involves government payers in assessment priority setting through criteria and discusses evidence with decision makers on the local context.

This report is adapted from presentations and discussions that occurred during ISPOR HTA and Patient Representative roundtables - Asia Pacific on 25 October 2019.

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Additional information

The next ISPOR Asia Pacific HTA and Patient Representative Roundtables will take place during the ISPOR Asia Pacific 2020 Conference, to be held on 12-15 September 2020 in Seoul, South Korea. For more information on these and other initiatives, please visit: www.ispor.org/member-groups/councils-roundtables.

The COVID-19 Virus in Wuhan, China: A Personal Story

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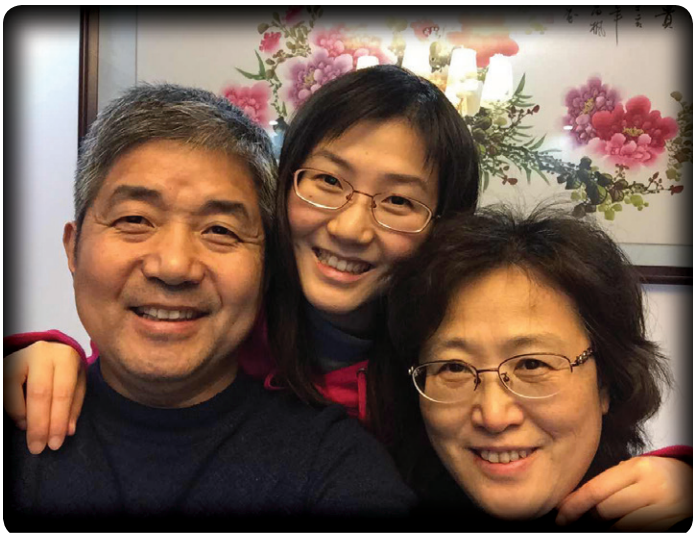
My mother has been hospitalized for 6 weeks with the COVID-19 virus. She lives in the epicenter of the outbreak in Wuhan, China. Since the outbreak of the epidemic, I have been closely following the news and the science. I have heard many frontline stories from my family and friends back in Wuhan. It has been an emotional rollercoaster ride for me, being a direct family member of a patient with the coronavirus. So, here is my story:

I grew up in Wuhan, China, which has, and will always have, a special place in my heart. It is where I spent the first 22 years of my life. Wuhan is where most of my family, relatives, and friends are. Wuhan is my home. Wuhan is my root. Wuhan may not be a well-known Chinese mega-city like Beijing or Shanghai, but it is a large metropolitan area with a population of 11 million. Wuhan is one of China's transportation hubs and is the financial, cultural, and educational center of central China. Since January 2020, Wuhan has been known, unfortunately, for another thing: the coronavirus.

> Despite being clearly symptomatic, she could not get tested for the virus due to the shortage of test kits. In my opinion, this was one of the biggest failures in the system in the early days, because without a positive test result, she could not get hospitalized.

It was the middle of December 2019 when I first read on a Chinese social media platform about a respiratory disease going around in Wuhan. At that time, the disease was simply classified as a "pneumonia of an unknown cause." I glanced through the article quickly and did not really pay much attention, as my years of PhD training in science have taught me not to trust such anecdotal stories easily. Two weeks later, the Chinese government, for the first time, confirmed the spread of the disease. Scientists identified the cause as a novel coronavirus. The official message was that there was no evidence of human-to-human transmission and the government had the situation under control, thus there should not be any reason to worry the general public.

This was reassuring to us because my family lives far away from the seafood market that was believed to be the source of the virus and they have always lived a healthy lifestyle. There should have been little chance of my family getting infected. My parents got on with their normal life; they had a few family gatherings and started to prepare for their upcoming trip to the United States to celebrate the Chinese New Year with my son, my husband, and me here in San Francisco.



From Left to Right: My father Weijin Zou, me (Siying Zou), and my mother Qiaoli Jia.

A month later, on January 14, 2020, we heard something concerning. A well-respected Chinese epidemiologist spoke at a national news briefing, confirming that the virus was being transmitted through human contact. In addition, there were already a number of cases of medical personnel becoming infected after caring for sick patients. Since then, we started to hear more and more heartbreaking stories—entire 3 generations of families getting infected and people dying in their homes because of the shortage of medical resources. My parents decided to cancel their US trip altogether given the growing severity of the situation.

A week later, on January 23, the central government locked down Wuhan. The local government suspended all forms of public transportation and banned all private transportation on the roads (except for emergencies). A city of 11 million turned into a ghost town almost overnight. Roads notorious for their traffic were empty. Shops across the city were closed. Only 2 types of business were allowed to remain open: pharmacies and supermarkets. Schools were postponed indefinitely. People were required to stay at home and order their food and daily groceries via community-based group purchases. In my parents' precinct, authorities even stopped the elevators in our 30-story apartment building to prevent people from going outside.

It was also on this fateful day that my mother started showing symptoms. She started having mild, transient fevers. Within a few days, her condition deteriorated drastically. She experienced high fevers (>105° F) that did not subside despite medication. In addition, she had difficulty breathing.

My father had to take her to the hospital. They chose to go to a hospital in the suburban area and left at 4:00 AM to try to avoid the peak hours of the hospital and minimize the risk of cross-infection. Based on my parents' recount, they were not prepared for what they saw: The hospital outpatient center was packed with hundreds of patients with fevers and coughs. The only way to get around was to push their way through the angry and anxious patients and their families.

After hours of waiting, my mother finally got a blood test and a computed tomography (CT) scan. Her CT images showed "ground glass" opacity in both lungs, a characteristic clinical marker of the coronavirus infection. My mother was immediately put on broad antiviral and fever-reducer infusion to try to alleviate her symptoms.

The following 4 days were the most challenging time for my family and me. My parents had to go to the hospital every day for the next 4 days for more infusions, but my mother kept getting weaker. Despite being clearly symptomatic, she could not get tested for the virus due to the shortage of test kits. In my opinion, this was one of the biggest failures in the system in the early days, because without a positive test result, she could not get hospitalized. What is perhaps more worrying is that my father did not have proper protective gear and was exposed to the dangerous environment every single day during her treatment. I felt scared and helpless for not being physically there for them.

I knew I could not just sit around and do nothing. I decided that while they were fighting for their lives on the frontlines, I would arm myself to the teeth with news and knowledge of the disease in order to be prepared to support my parents in any possible way. I read up on the virus and any related ongoing research. I learned that there were a number of drugs in clinical trials that might work for this disease. One of the most promising drugs is remdesivir from Gilead. I reached out to the physician lead of the trial, hoping to get my mother recruited (I never heard back). I even contacted Gilead for compassionate use but learned that it was not feasible due to multiple regulatory issues. I reached out to nearly all of my contacts in China to see if they could help my family and to see if there was any chance to escalate my mother's case so she could get hospitalized as soon as possible.

> The United States could be only just weeks or even days away from an outbreak that could spin out of control. I am also worried that the US healthcare system will be overwhelmed.

Ultimately, we got lucky. On the fourth day of infusion, my mother was able to get a confirmed diagnosis by the nucleic acid test. On the same night, my parents got a phone call telling them there was a hospital bed ready for her. My father had to bring her in within an hour to secure the bed before it was given to another patient.

Long story short, my mother has been hospitalized for more than 6 weeks. She received oxygen and was stabilized. Her condition has improved with the comprehensive hospital care. Her most recent tests showed that the viral load was already undetectable. However, she is still recovering from lung and heart damage inflicted by the virus and may need to stay in hospital for a while longer. My father, because of his close contact with my mother and other patients with the coronavirus, was put under strict home quarantine for 14 days. He could not even open the door to take out trash. Miraculously, despite everything he went through to get care for my mother, he has been doing well, and multiple testing for the virus showed that he did not get infected at all.

It has been almost 3 months since the virus outbreak in China. The situation in Wuhan has gotten much better. The numbers of new domestic cases and deaths have been in the single digits for 5 consecutive days. On the other hand, we are seeing the virus sweep across other countries like Italy, Spain, and the United States.

A lot of people have asked me what I think about the situation in the United States, especially after what I have been through. I told them I am worried. I am worried about the limited number of coronavirus tests available. In addition to social distancing, getting tested early to identify the infected, isolating them, and tracking whom they have been in contact with are the only ways to slow down the spread of the disease. Without enough testing capacity, doctors are hamstrung and the health of the general public is endangered.

I am also worried that a large portion of the general public is not giving enough attention to the issue or is treating it cavalierly. The Asian community in the United States generally seems to be more vigilant, but many more Americans still think of it as "just another flu." That is not right. COVID-19 is a novel virus with still many unknowns. We do not have an effective treatment or vaccine. As a species, humans have never encountered the virus before and, therefore, have no immunity. Despite draconian measures, the virus still took a big toll on China and the Chinese people and is already putting countries like Italy and Iran in an unprecedented public health crisis.

The United States could be only just weeks or even days away from an outbreak that could spin out of control. I am also worried that the US healthcare system will be overwhelmed. This is a scenario that has been played out repeatedly over the past few months: A highly contagious novel respiratory disease, if not controlled, sweeps through an unimmunized and unprotected human population, resulting in an unprecedentedly high influx of patients that strains most, if not all, medical institutions quickly. And that has led to many heartbreaking stories.

Finally, I worry that some people will use the coronavirus as another convenient excuse for racism and xenophobia against people of Asian descent. The COVID-19 virus is now a pandemic. It is global. The virus knows no borders; it does not discriminate based on nationality, ethnicity, or language. We are all in the same boat. Humanity has to unite and fight this war together as one.

Update: After 7 weeks of hospitalization, my mother finally got discharged on March 25th. She has been sent to a hotel for an additional 14-day quarantine, as mandated by the Chinese government. We are deeply grateful to all the people who have given us all forms of support and help during this difficult time. Special thank you to all the doctors and nurses around the world who had fought and are still fighting on the frontlines of the coronavirus pandemic.

THE STATE OF HEALTH TECHNOLOGY ASSESSMENT

BY MICHELE CLEARY

AS NEW DRUGS AND HEALTH TECHNOLOGIES EMERGE, often with exceedingly high price tags, health payers and other decision makers are increasingly reliant on health technology assessment (HTA) to navigate the balance between access and affordability. Health payers, hospitals, doctors, medical groups, and more are wrestling with the same basic questions of how to make the best use of limited resources, and how to try to make sure that prices align with the benefits for patients.

Healthcare decision makers are increasingly reliant on HTA as a way to evaluate clinical and economic evidence to help improve cost containment and quality, guide more effective delivery of care, and decrease the use of programs or treatments that are ineffective. This month's feature article examines differences in how HTA has been implemented globally, highlighting common concerns and future objectives.

Canada: CADTH and Beyond

Brian O'Rourke, BSc (Pharm), PharmD, president and CEO of the Canadian Agency for Drugs and Technologies in Health (CADTH), summarized his view of HTA organizations around the world, "If you've seen one HTA, you've seen one HTA. We all differ based on our governance, whether we're part of government or not-for-profit, how we're funded, the transparency that we have, and the scope of work. Some are specifically focused on devices and some are specifically focused on drugs and some have a much broader portfolio covering both and even public health interventions."

O'Rourke considers CADTH to be more of a full-service HTA agency, evaluating pharmaceuticals, medical devices, medical, dental, surgical devices, procedures, programs and diagnostics—basically, any clinical intervention where there is a need for evidence to support a reimbursement of that particular intervention.

Established in 1989 as the Canadian Coordinating Office for Health Technology Assessment (CCOHTA), CADTH originated as an independent, not-for-profit government organization aimed at improving coverage decisions to ensure appropriate and cost-effective healthcare for all Canadians.

Canada's Common Drug Review

In the 1990s, CCOHTA expanded its scope to include pharmaceuticals, incorporating economic methodologies to its clinical evaluations. CADTH created the Common Drug Review in 2003, providing a pan-Canadian approach to reviewing new drugs and new drug indications. The Common Drug Review is firmly established as part of Canada's drug review process. Upon receiving market approval from Health Canada, manufacturers make a submission to the Common Drug Review for an HTA recommendation. Public drug plans across Canada use these recommendations in making their coverage decisions, with the Common Drug Review recommendation often forming the basis for drug price negotiations by its pan-Canadian Pharmaceutical Alliance.

Patient input is sought for each drug that is reviewed by the Common Drug Review. This input is discussed during expert committee deliberations and reflected within the final reimbursement recommendations. The final recommendations are published in full so patients can understand how their input was incorporated into the process.

Commitment to transparency

Today, CADTH's recommendations extends beyond traditional assessments of new drugs and technologies and now advances a life-cycle approach to HTA, providing early scientific advice to industry, undertaking reassessments of drugs after they are listed, conducting condition-level reviews, and integrating real-world evidence into drug reviews.

"One of the things we learned very early on as the agency evolved through the years was the need to provide methodology guidelines and be very transparent about the work we do," O'Rourke said. CADTH publishes its assessment guidelines (now in its 4th edition), outlining how it conducts its economic evaluations for all of the technologies, including orphan drugs. O'Rourke noted that these are downloaded 10,000 to 12,000 times every year in Canada.

Expanding stakeholder engagement

To expand transparency, CADTH launched its patient engagement program for its drug reviews in 2010 to ensure that patient perspectives regarding orphan drugs, gene and cell therapies, and other disruptive technologies were captured.

CADTH now includes patient and community advisory committees with broad representation from different disease areas, as well as different cultures from across Canada to identify "patient-important" outcomes and expectations for new treatments and to inform the development of research protocols. "We engage patients to help better understand the outcomes that are important to them, and that data need to be captured in that clinical trial," O'Rourke said. "They also provide good advice on how we can best engage with the patient community."

However, going forward, he wants CADTH to expand involvement of other stakeholders, namely clinicians, physicians, pharmacists, nurses, and physiotherapists. "If the policy and the clinical practice go hand in hand, it's a much smoother transition into the reviews and the reimbursement recommendations," said O'Rourke.

Other Canadian approaches: HTA in British Columbia

HTA in Canada extends beyond CADTH, as a recent survey identified 44 different HTA organizations within Canada. One such example is the University of British Columbia's Therapeutics Initiative. In 1994, the British Columbia Ministry of Health, concerned about both the increased use of prescription medications and the introduction of new (and often expensive) drugs, partnered with independent, academic researchers at University of British Columbia to establish the Therapeutics Initiative.

Therapeutics Initiative created an outcomes-based, decision-making framework that supports responsible funding decisions in the province, using published literature, Cochrane Collaboration meta-analyses, and scientific material presented by the pharmaceutical industry. Mitch Moneo, BA, Assistant Deputy Minister, Pharmaceutical Services Division, noted, "The key consideration of public coverage in British Columbia is quality and published evidence of comparative mortality or morbidity benefit."

Prioritizing patient voices

British Columbia's Drug Benefit Council reviews evidence generated by CADTH and Therapeutics Initiative, while also considering input garnered from patients, caregivers, and patient groups submitted through an online questionnaire called Your Voice. Input from these critical stakeholder groups helps contextualize the national CADTH recommendations for British Columbia.

As with many HTA organizations, orphan drugs pose a significant challenge to Moneo's organizations. The evidence associated with the regulatory approval of most orphan drugs is very sparse, creating a lot of uncertainty for public and private payers. Yet, evaluation of how these types of drugs and disruptive technologies support patient outcomes is consistent with the core values of the Canadian system.

Opportunities and challenges of real-world evidence

British Columbia has joined other Canadian jurisdictions to explore wider use of real-world evidence for their HTA evaluations. "The methods for selecting candidates and assessing the real-world evidence are being explored," Moneo said. "For example, methods for rapid expected value-of-partial-perfect-information are used to determine (at an early analytic stage) if there is a positive social value to real-world evidence generation through research-oriented market access; methods for simulation models for drug uptake and real-world evidence generation are being constructed to identify the optimal design and terms of a market access agreement; and methodologies to facilitate iterative Bayesian updating of prior parameter distributions (including bias adjustment and advanced evidence synthesis components) are being explored.

However, Moneo sees limits to the use of real-world evidence in his organization. "The concept of using pragmatic trials and patient registries and routine administrative databases to assess the impact of therapy may have some merit, but what it means in terms of scientific rules of evidence isn't clear." He continued, "It's a bit troubling that there is a growing expectation that HTA organizations and payers will now undertake work that has essentially been the domain of traditional phase III clinical trials."

> How we are going to pay for all of these technologies in a sustainable way? That's going to require new ways of thinking, new managed entry agreements, new assessments across the life cycle of technology. No one agency is going to be able to do this themselves.
> – Brian O'Rourke

Regulatory changes on the horizon

Moneo did highlight upcoming regulatory changes in Canada. On July 1, 2020, a newly amended Patented Medicines Regulations will come into effect, establishing new value thresholds.

Canada's Patented Medicines Review Board is proposing a guideline that sets a pharmacoeconomic value threshold of $60,000 per quality-adjusted life year, adjusted by market size. Also noteworthy, for patented medicines with an estimated total prevalence no greater than 1 in 2000 across all approved indications, the allowable drug price will be set at 50% above the threshold (but further adjusted for market size if the patented medicine realizes annual revenues in excess of $12.5 million). In theory, this national value threshold may mitigate the burden of risk associated with orphan and other high-cost drugs, but not without controversy. Industry and patients have expressed fear that regulatory value thresholds will impede Canadians' access to important medicines.

Taiwan

Taiwan has been conducting HTAs since 2007 following the creation of the Division of Health Technology Assessment within the Center for Drug Evaluation. The HTA findings support the National Health Insurance Administration's reimbursement and drug coverage decisions (the group is not directly involved in price determination). "The ultimate goal of the HTA program is to support the health authority to maximize public health benefits," noted Churn-shiouh Gau, PhD, Executive Director of the Center for Drug Evaluation.

The HTA team primarily assesses the clinical comparative effectiveness and economic evaluation of new drugs and medical devices, providing pre- and postmarket evaluations to support the National Health Insurance program's decision making. The team also conducts various HTA-related research projects commissioned by other health authorities under the Ministry of Health and Welfare. The HTA program was extended to include medical devices in 2011, medical services in 2014 , and social care in 2016.

Patients views have long been a national priority

Gau stated that patient engagement has been a priority since 2013, when the National Health Insurance Act mandated that patient participation in its insurance coverage decisions. Patient participation in HTA began in 2015. The online platform, Patient

Opinions for New Drugs and New Medical Devices, allows patients and advocacy groups to provide opinions about drugs and medical devices currently being evaluated.

Since 2016, more than 20 face-to-face talks or focus groups have been hosted by the Center for Drug Evaluation HTA team, with more than 300 patient participants sharing their perspectives. Participating groups have included the Chinese National Association of Deaf, Taiwan MPS Society, the Rheumatoid Arthritis Aid Group of the Republic of China, and the Hemophilia Association of Taiwan.

United States: ICER

As with much of its healthcare system, the United States has taken a different approach to HTA. No formal health technology assessment body resides in the United States to evaluate the value of new drugs. Instead, the United States relies on multiple stakeholders (eg, pharmacy benefit managers, payers, providers, and manufacturers), each using different measures to determine the value of new products. However, as payers and policy makers have begun to scrutinize prescription drug prices, Steven D. Pearson, MD, MSc, founder and president of the Institute for Clinical and Economic Review (ICER), has filled the void of a designated HTA in the United States.

Like previously mentioned HTA organizations, ICER uses publicly available information, clinical trials data, and other manufacturer-provided information to conduct pharmacoeconomic analyses to inform payers and policy makers.

> In our common quest to find the ideal in fair pricing, fair access, and future innovation, we have to learn from each other. –Steven D. Pearson

HTA in United States mirrors its decentralized health system

However, it is also a reflection of the US health system. Pearson noted, "In the United States, with a very chaotic or pluralistic insurance system and with a generally higher distrust of centralized decision making over markets, it's been more natural for the system not to evolve towards having a centralized kind of federal process for evaluating evidence, whether you want to call it comparative clinical effectiveness or cost-effectiveness." He continued, "I think we're on our own unique, distinctive journey. The United States is a very different system and we can't just copy and paste what other countries do."

Addressing the question of "fairness"

ICER was founded as a laboratory to experiment with methods to determine and discuss value so that the public could participate in creating a higher value health system. Pearson spoke of the "great eternal question" of HTA, that is, Is it fair to everybody? Sensitive to the issue of fairness, ICER adheres to a very formal process of introducing their methods to public comment.

However, Pearson noted the challenge with engagement in HTA is when and how long to engage. "It's still been a learning process for them and for us, ensuring that we make that engagement as meaningful as possible. We have to start out saying that we really don't know the diversity of experience with this condition, what value really feels like to patients and to their families and what do we, and what can we learn from that?"

Pearson continued, "We almost always find that some of the most important aspects of value aren't captured in the clinical data from the trials that are done before FDA (US Food and Drug Administration) approval. And so we're trying to figure out how to either qualitatively or quantitatively build that into our assessments so that ultimate decision makers can really keep that in view. So, we really need the patients, and as time goes on, we need to continue to find ways for their input to be tangible, visible, and very influential."

Importance of transparency

Pearson highlighted ways he felt ICER is distinctive, stressing transparency and stakeholder engagement. "Our approach allows end users to feel confident that our reports have gone through a rigorous scientific process, as well as a full public engagement process. I think that's the key to our being distinctive rather than the kind of cost-effectiveness modeling that we do, which others can do as well." He continued, "We do have some distinctly different methods for looking at treatments for ultra-rare disorders, as well as ones that we've just announced this past year on high-impact single- or short-term therapies, things that some people would call potential cures."

Pearson noted that ICER uses state-of-the-art cost-effectiveness methods, embedded in a kind of "distinctive approach to public deliberation that acknowledges other dimensions of value and contextual issues." ICER publishes its formal list of criteria on its website, noting how it prioritizes those technologies where there will be a paradigm shift in care. He said that he finds few groups doing that kind of constellation of approaches, creating trustworthy, publicly available research. And that was by intent. "We really wanted our work to be the starting point for a public kind of deliberation on value." He continued, "I think we've gained a stature through our experience and through people's view of the scientific rigor of our work. That means that there really aren't other groups that are doing work for applied health technology assessment in the same way."

Future applications of real-world evidence

Pearson stated that ICER tries to keep its ears open and respond honestly to a criticism. He added, "Criticism is very healthy, and we don't seem to ever be short of it. That's one of the benefits to us not being a governmental agency. We certainly feel like we can be flexible and listen and experiment in ways that hopefully can be quick and responsive to the needs of the, the communities that we hope to, to help."

Like Moneo, Pearson expects real-world evidence to play a larger role in HTA despite its challenges. "It's going to be a challenge for us in terms of how often we update our reviews, what data sources are used, and how do we do it in a way that is transparent and trustworthy. But my gut tells me we are going to continue to innovate and have exciting new platforms for treatment that are going to challenge us to figure out how to use them clinically and how to pay for them is going to increase the need."

"Ultimately it does serve everyone's interest to have good evidence, to have high bars for good evidence, to really reward good science, good innovation, and to reward it in proportion to the ability to help patients," he concluded.

Future challenges

With a consistent stream of innovative new therapies, HTA organizations are challenged to determine ways that health systems can pay for new technologies in a sustainable way. And the pressure for HTA will grow with the threat of economic recessions. These market forces will increase the pressure for HTA organizations to figure out how to align the prices better with the benefits to patients and to make sure that this continues to provide enough incentives for robust innovation.

"How we are going to pay for all of these technologies in a sustainable way? That's going to require new ways of thinking, new managed entry agreements, new assessments across the life cycle of technology," said O'Rourke. "No one agency is going to be able to do this themselves."

Many international jurisdictions have developed and implemented new approaches to assess value with various degrees of success. We need to learn from others' experience and share knowledge. Pearson summed up things this way, "In our common quest to find the ideal in fair pricing, fair access, and future innovation, we have to learn from each other. I think the positives can certainly outweigh the short-term contest that we often feel that we're engaged in when we're talking about one specific drug or one specific other kind of intervention."

About the Author

Michele Cleary is a HEOR researcher and scientific writer with more than 15 years of experience in the healthcare field.

Suggested reading:

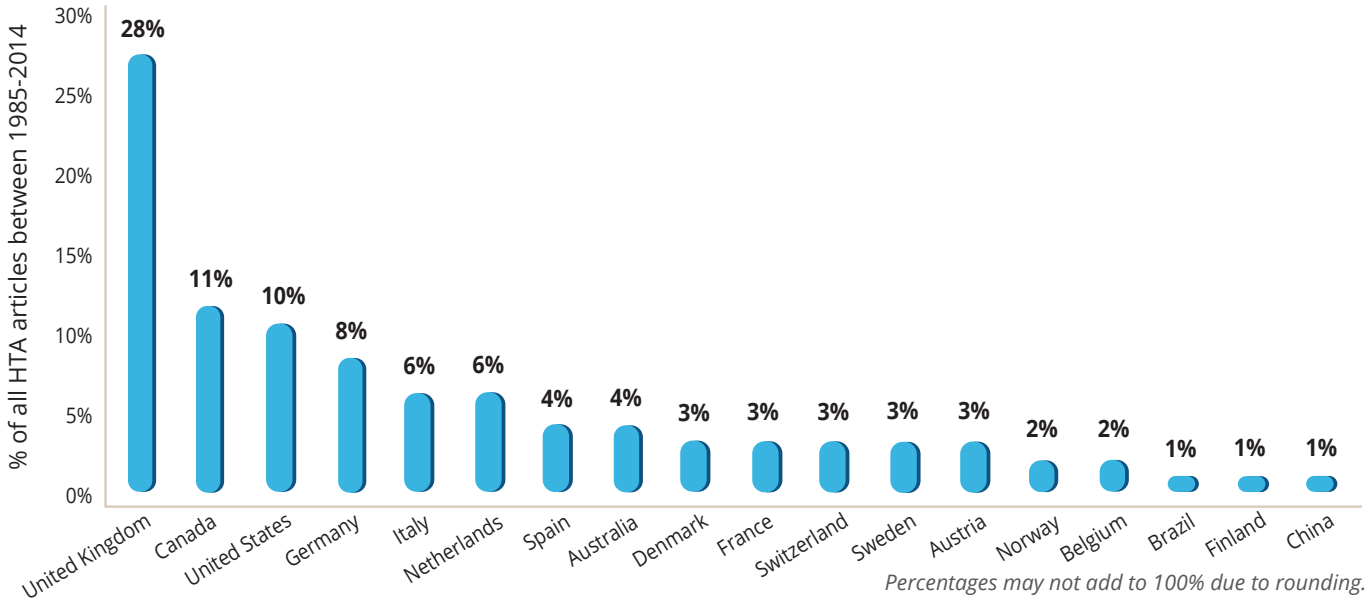
Value in Health Themed Section: HTA Around the World: Influences of Culture, Values, and Institutions [January 2020]

- HTA Around the World: Broadening Our Understanding of Cross-Country Differences
  Aleksandra Torbica
- The Emerging Social Science Literature on Health Technology Assessment: A Narrative Review
  Olga Löblová, Trayan Trayanov, Marcell Csanádi, Piotr Ozierański
- Differences in Health Technology Assessment Recommendations Among European Jurisdictions: The Role of Practice Variations
  Rick A. Vreman, Aukje K. Mantel-Teeuwisse, Anke M. Hövels, Hubert G.M. Leufkens, Wim G. Goettsch
- Do Social Values and Institutional Context Shape the Use of Economic Evaluation in Reimbursement Decisions? An Empirical Analysis
  Aleksandra Torbica, Giulia Fornaro, Rosanna Tarricone, Michael F. Drummond
- Economic Evaluation for Pricing and Reimbursement of New Drugs in Spain: Fable or Desideratum?
  Juan Oliva-Moreno, Jaume Puig-Junoy, Marta Trapero-Bertran, David Epstein, Carme Pinyol, José Antonio Sacristán
- Increasing the Legitimacy of Tough Choices in Healthcare Reimbursement: Approach and Results of a Citizen Forum in The Netherlands
  Leon Bijlmakers, Maarten Jansen, Bert Boer, Wieteke van Dijk, Stef Groenewoud, Jacqueline Zwaap, Jan-Kees Helderman, Job van Exel, Rob Baltussen
- Role of Culture, Values, and Politics in the Implementation of Health Technology Assessment in India: A Commentary
  Shilpi Swami, Tushar Srivastava
- Formal Implementation of Cost-Effectiveness Evaluations in Japan: A Unique Health Technology Assessment System
  Masataka Hasegawa, Shigekazu Komoto, Takeru Shiroiwa, Takashi Fukuda

By the Numbers: The State of Health Technology Assessment (HTA)

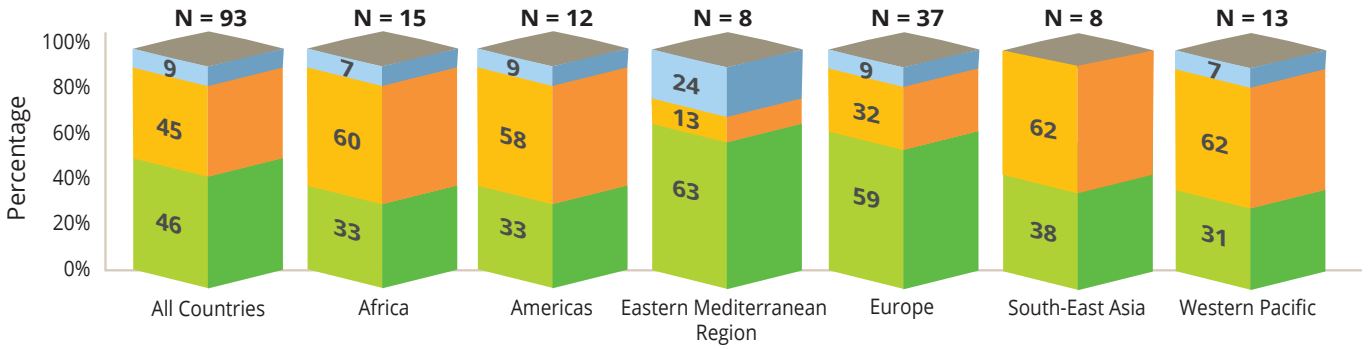
Section Editor: The ISPOR Student Network

Country-Specific Distribution of HTA Publications, 1985-2014[1]



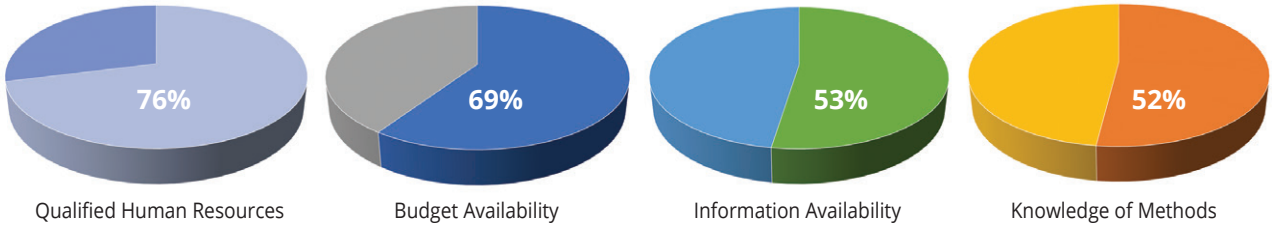
Percentages may not add to 100% due to rounding.

Percentage of World Health Organization Member Countries With Legislative Requirements to Consider the Results of HTAs (total and by region)[2]



Footnotes: 1) "N" represents the number of countries surveyed overall and by region.
2) Responses were given by an individual from the national HTA board appointed by Ministry of Health of the country.

Top 4 Barriers in Conducting HTAs for Decision Making: A Survey of 111 World Health Organization Member Nations[2]



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Acknowledgment: We would like to thank Zeba Khan, RPh, PhD for her review and helpful comments

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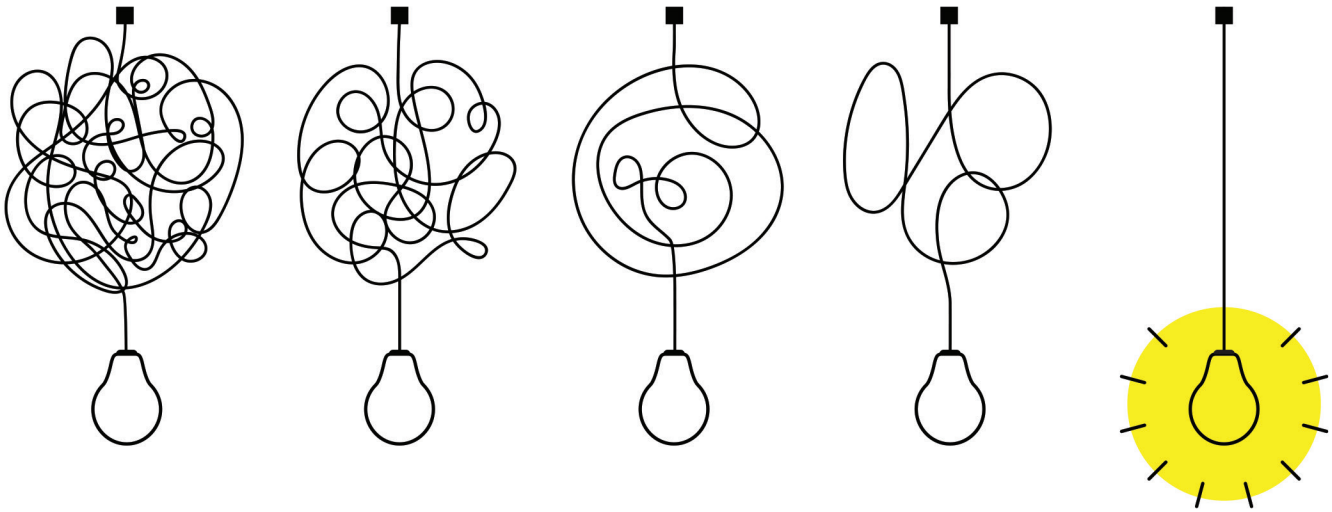

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Are Missing Data Properly Accounted for in Health Economics and Outcomes Research?

Gianluca Baio, PhD, MSc, University College London, London, England, UK; **Necdet B. Gunsoy, PhD, MPH**, Global Market Access and Pricing, AbbVie, Maidenhead, Berkshire, UK; **Nneka Onwudiwe, MBA, PharmD, PhD**, US Food and Drug Administration, Silver Spring, MD, USA; and **David J. Vanness, PhD**, The Pennsylvania State University, State College, PA, USA on behalf of the ISPOR Missing Data in HEOR Working Group of the ISPOR Statistical Methods Special Interest Group

The ISPOR Statistical Methods in Health Economics and Outcomes Research (HEOR) Special Interest Group investigated how missing data impact the analysis of HEOR data, and the potential of using full Bayesian methods to account for partially recorded information in the broader context of economic modeling.

When critical data go missing

When the ISPOR Statistical Methods in Health Economics and Outcomes Research (HEOR) Special Interest Group (SIG) convened to choose its first key project, members of the leadership group expressed interest in developing guidance for a variety of statistical approaches. One theme emerged as both central to, and uniquely challenging in, our field: how to deal with missing data, particularly in the context of real-world evidence.

Much of the field of HEOR boils down to the process of making statistical inference from clinical and economic data so that decision makers can assess the value of medical care. The rules for making valid inference are challenging enough in the world of clinical trials, where outcomes are assessed under carefully controlled conditions in idealized settings designed to capture all necessary data. While such randomized controlled trial data are used in HEOR, we also often contend with complex patterns of treatment delivery, each treatment having potentially heterogeneous effects, and resulting in multiple causally interconnected outcomes. Many of our outcomes are subjective, noisy, and logistically or economically burdensome to collect.

Many of our data sources were designed to facilitate clinical care, or generate bills conforming to administrative rules and not for conducting scientific research. The very nature of data used in our field both makes missing data more likely, and amplifies its potential to create bias.

Rubin provides a useful framework for understanding missingness.[1] Imagine that there's a process that gives rise to the complete, idealized, true dataset—everything we need to conduct valid inference for our purpose. Now, imagine a second process that causes some of those data to be deleted. It might be entire variables that go missing for everyone, or they might be missing for some individuals, but not others. Some individuals might be missing all their data and it's as if they never existed, while others are missing only some variables. In the context of longitudinal data, such missingness may come and go, or it may persist. The patterns themselves are interesting, but it is how the data went missing in the first place that matters most.

When the process that caused the data to go missing is unrelated to the process that generated the true dataset, we say that data is "missing completely at random." In this case, ignoring observations with missing data reduces our inferential power, but it does not create bias; the estimate effect remains unbiased but its precision decreases (standard error increases). We can make up for it by just collecting more of the same data. Sometimes, the process that caused the data to go missing is related to the process that generated the true dataset, but in a way we can control for by using data we actually observed. We term this process "missing at random;" the observed data are reweighted and missing values are imputed based on their relationship to the observed data.[2] Alternatively, we may attempt to model the 2 processes explicitly. But when the process that caused some of the data to go missing depends on the missing data themselves, things get especially challenging. In this case, we say that the underlying generating process is "missing

> ...a full Bayesian model accounting for missing data extends the industry standard tool of "multiple imputation," where missing values are replaced by simulations obtained from the whole system of modelling assumptions.

not at random," and we need to appeal to "extra-statistical" assumptions about the missing data process in order to improve our chances of getting our inference correct.

Our key project is reviewing and synthesizing the methods literature to see what approaches have already been used and assessed in HEOR and, in addition, what we can adapt from other fields to suit our unique challenges in HEOR.

Preliminary literature review

A literature review was conducted to understand methodological approaches used to account for missing data in cost-effectiveness analyses specifically. Studies were eligible only if they focused on addressing missing data for costs, health-related quality of life (HRQoL) measures, or utility.

We conducted the search in PubMed. Identified records were screened independently by authors Gunsoy and Baio. Data from eligible abstracts were then extracted by volunteers from the SIG membership. A total of 16 studies were identified for which information on the context, missing data, and method(s) used were extracted.

Identified studies were mainly conducted in clinical trials, addressing either missing cost, HRQoL, or both jointly, and evaluated multiple imputation. The majority of studies were focused on imputing outcomes rather than explanatory factors. Although most studies applied multiple imputation, a large variety of model specifications were observed.

Practical guidance on how to handle missing data

Table 1 presents a list of recommendations from 3 published studies identified in the literature review that address missing data within the context of a clinical trial. The 3 studies were chosen because of their relevance to handling missing data in the field of HEOR and for decision makers tasked with comparing and choosing among available treatment options. As a practical guide, the studies presented recommend that sensitivity analysis be performed to determine to what extent trial results change to different missing data assumptions. The cost-effectiveness analysis-based studies in Table 1 recommend 2 model-based "missing not at random" methods to handling sensitivity analysis, the selection models and pattern mixture models approach.

Next steps

As suggested by recent reviews,[3,4] over the past few years the HEOR literature seems to have caught up with other research fields in understanding the importance of correct reporting, analysis, and statement of limitations when it comes to recommendations for decision making based on data affected by missingness.

However, HEOR data are characterized by extra complexity, including a bivariate outcome (clinical benefits and costs), whose components are likely to be correlated and characterized by asymmetric distributions and spikes (eg, excess of 0 costs or 1 utilities). Failure to properly account for these elements may produce output from the underlying statistical model that possibly underestimates the underlying uncertainty in the actual cost-effectiveness profile of a given intervention. This in turn has the potential to make the whole decision-making process flawed, as it is clearly based on untenable premises.

The way forward is to embrace this complexity and use statistical methods that are suitable to deal with the many nuisances of the data we analyze. In particular, Bayesian methods are increasingly popular in HEOR,[5-7] (eg, when dealing with network meta-analysis and evidence synthesis[9], analysis of survival data[10] and decision making in general[8]) and are a promising tool to deal with missing values.

In a nutshell, the fundamental feature of a Bayesian analysis is that uncertainty is modeled using the language of probability distributions. Much as in a standard, "frequentist" analysis, sampling variability surrounding the observed data is modelled using a distribution (eg, a Beta distribution to model quality-adjusted life years [QALYs], or a Gamma distribution for the observed costs). However, a Bayesian analysis implies a probability distribution for any quantity that is not deterministically known. This includes: (a) *model parameters* (eg, means, population incidence, etc) that we shall never be in a position of observing directly; and (b) as *yet unobserved data* (eg, that can be obtained using real-world evidence produced by registries of clinical practice). These may or may not be available in the future and thus we are still uncertain about what their value will be.

In a Bayesian sense, the missing data process is simply another part of a wider model, which considers the 2 outcomes of interest, as well as any other relevant covariate. The objective of the analysis is to specify a joint probability distribution for the (partially) observed data (including benefits, costs, and a missingness indicator) and the model parameters, which typically indicate the population average costs and benefits. Modeling assumptions are made explicit in terms of *prior* probability distributions describing possibly subjective

Our key project is reviewing and synthesizing the methods literature to see what approaches have already been used and assessed in HEOR and, in addition, what we can adapt from other fields to suit our unique challenges in HEOR.

knowledge on the model parameters, as well as probability distribution to describe variability in the (partially) observed data. Combining these with the evidence provided by the data, we can revise our assessment of the uncertainty underlying the unobserved quantities in the model (eg, the population average costs and benefits). The updated, *posterior* distribution can then be used directly to aid the decision-making process.

Of MICE and missing data

In effect, a full Bayesian model accounting for missing data extends the industry standard tool of "multiple imputation," where missing values are replaced by simulations obtained from the whole system of modelling assumptions. In fact, Rubin's original ideas were arguably very Bayesian in nature, but

Table 1. Handling Missing Data Within the Context of a Clinical Trial

Publication Year	Study Objective	Outcome Measure(s)	Recommendations
2014	A review article (Faria et al) that provides guidance on how to handle missing data in within-trial CEAs following (i) a plausible assumption for the missing data mechanism; (ii) the method chosen for the base-case; and (iii) sensitivity analysis	CEA	**Stage 1:** Descriptive Analysis of Missing Data Mechanism **Descriptive analysis of the missing data** 1) Amount of missing data by trial group at each follow-up period 2) Missing data patterns 3) Association between missingness and baseline variables 4) Association between missingness and observed outcomes **Stage 2:** Choosing Between Alternative Methods Given Their Underlying Assumptions **Handling Missing Baseline Values** 1) Mean imputation and MI are suggested options **Complete Case Analysis, Available Case Analysis, and Inverse Probability Weighting** 1) CCA and available case analyses are valid under MCAR 2) CCA is a good starting point and benchmark but not for the base case 3) Available case analysis makes more efficient use of the data compared to CCA 4) IPW is suitable for a monotonic pattern of missing data **Single Imputation** 1) Mean imputation valid for missing baseline variables 2) Conditional regression imputation assumes MAR but can affect the cost-effectiveness estimate 3) Last-value carried forward (LVCF) can bias parameter estimates 4) Single imputation methods are not appropriate to handle missing data on outcomes **Multiple Imputation** 1) MI can handle both monotonic and nonmonotonic missing data under MAR and can be modified to handle MNAR 2) Two approaches to implementing MI: joint modelling (MI-JM) and chained equations (MICE) 3) MI-JM assumes multivariate normal distribution 4) MICE accommodates non-normal distributions, allows for interactions and nonlinear terms, and incorporates variables that are functions of imputed variables 5) MICE can handle datasets with a large number of variables with missing data 6) MICE is more applicable to missing data in within-trial CEAs **Likelihood-Based Methods** 1) Likelihood-based models assume MAR conditional on the variables, unless MNAR is explicitly modeled 2) Likelihood-based methods can produce similar results to MI when all variables that relate to missingness are included in the analysis model 3) Relies on the correct specification of the model; the impact of different specifications should be compared and reported **Stage 3:** Methods for Sensitivity Analysis to MAR Assumption 1) Selection models and pattern mixture approaches 2) Selection models using a weighting approach tends to fail for large departures from MAR
2018	A review article (Leurent et al.) to determine the extent of missing data, how they were addressed in the analysis, and whether sensitivity analyses to different missing data assumptions were performed in studies identified. Also, to provide recommendations to improve practice.	CEA	**Prevent** 1) Maximize response rate (consider questionnaire design, mode of administration, reminders, incentives, participants' engagement, etc.) 2) Consider alternative data sources (eg, routinely collected data) 3) Monitor cost-effectiveness data completeness while trial ongoing **Primary** 1) Formulate realistic and accessible missing data assumption for the primary analysis (typically, but not necessarily, a form of the missing at random assumption) 2) Use appropriate method valid under that assumption (typically, but not necessarily, multiple imputation or maximum likelihood) **Sensitivity** 1) Discuss with clinicians and investigators to formulate plausible departures from the primary missing data assumption 2) Consider a broad range of assumptions, including missing not a random 3) Use appropriate method valid under these assumptions (typically, but not necessarily, pattern-mixture models or a reference-based approach) **Report** 1) Report the number of participants with cost and outcome data, by arm and time-point 2) Report possible reasons for nonresponse and baseline predictors of missing values 3) Describe methods used, and underlying missing data assumptions 4) Draw overall concusion in light of the different resuts and the plausabiity of the respective assumptions
2018	A review article (Rombach et al.) that provides guidance on the choice of MI models for handling missing PROMs data based on the characteristics of the trial dataset, specifically with regards to the use of MI.	PROMs	1) Imputation at the item level may not be feasible for small sample sizes and/or larger proportions of missing data 2) Smaller samples with large amounts of missing data, imputation at the composite score level is more beneficial when there is a predominantly unit-nonresponse pattern 3) When performing imputation at the item level using ordinal logit models, the dataset should be investigated thoroughly for low count and potential problems due to perfect prediction 4) Ideally, imputation at the item/subscale level may provide more precise estimates of treatment effect compared to the imputation at the composite score level or CCA but it's often unfeasible and prone to convergence

Abbreviations: CCA indicates complete cases analysis; CEA, cost-effectiveness analysis; IPW, inverse probability weighting; MAR, missing at random; MI, multiple imputation; MICE, multiple imputation by chained equations; ML, maximum likelihood; MNAR, missing not at random; PROMs, patient-reported outcome measures.

at the time, there simply wasn't the computer power and methodology to perform the computations.[1] Thus, commonly used methods (eg, multiple imputation by chained equation, [MICE])[11] are based on a hybrid of Bayesian grounding and frequentist implementation. Crucially, these methods are often devised for modelling structures that are slightly simpler than those we need to face in HEOR (eg, when the interest is only in a single outcome variable or when the data are more well-behaved and can be reasonably modeled using normal distributions). For this reason, expanding them to a full Bayesian approach may be a very attractive way forward for our field. This, coupled with the increasing drive to using suitable statistical software and appropriately sophisticated models throughout the statistical and economic analysis, indeed has the potential to improve the decision-making process.

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

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Additional information

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Estimating Comparative Effectiveness When Patients Are Switching Treatments: A Real-World Challenge

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Treatment switching makes estimation of comparative effectiveness a challenge in observational studies. Even though useful analytical methods abound, these rely on assumptions that can't easily be tested and on data that are not always collected.

Switching happens

A patient will be naturally inclined to initiate, change, or discontinue their treatment if they (or their physician) are not happy with the results, are experiencing adverse reactions or tolerability issues, or when better treatment options become available. This is true of both clinical trials and in the real world. Flexibility in treatment, whilst beneficial for the individual patient, poses challenges to prescribers and payers. How can they compare the effectiveness of treatments when patients are switching? "Not easily" is the glib answer. Treatment switching in any clinical trial setting complicates comparisons of therapies. Payers need to know what the "bang" is in their "bang-for-bucks" pharmacoeconomic calculations and/or the added benefit over standard treatment options. But how are these stakeholders to evaluate comparative effectiveness in messy, real-life situations?

Challenges

Importantly, and for good reason, treatment switching is limited in most randomized controlled trials. As the study label implies, switching treatments, if it does arise, usually happens under controlled conditions. However, the same cannot be said of patients in real-world, observational settings. Here switching is mainly left up to the patient and their treating physician, which usually makes it more difficult to address. This poses severe challenges for payers who are increasingly reliant on the use of observational "real-world" data to inform their decisions.

Treatment switching shouldn't necessarily be regarded as a problem. Patients change treatments in randomized controlled trials for a variety of reasons, (eg, their disease may progress or they may suffer a treatment-related adverse event). If they switch to another treatment that is widely available then, from a pragmatic perspective, this does automatically lead to a health technology assessment (HTA) complication. The switch simply reflects what would have happened in reality. Problems only arise if patients switch to treatments that are not widely available and not part of the standard treatment pathway. In such cases we cannot observe from unadjusted trial results what effect the switch has had.

In observational studies the problems are similar, but more extensive. Non-standard treatment pathways remain problematic, such that any meaningful interpretation of these without the necessary statistical adjustments is difficult. Moreover, there are usually no (or much less stringent) eligibility criteria, no randomization, and a lack of a clearly defined baseline. Patients may initiate the treatment of interest at different time-points in relation to their disease. Hence, before attempting to address treatment switching, we first need to consider how to conduct a statistical analysis comparing 2 or more treatments when we know that patients might have very different characteristics affecting their prognosis (leading to channelling bias, confounding by indication).

Intention-to-treat...?

Randomized controlled trials are typically analyzed following the intention-to-treat principle. Intention-to-treat analyses aim to provide an unbiased comparison of randomized groups, but do not make any adjustments for treatment changes. Hence, it's implicitly assumed that switching occurs randomly. While it remains common for HTA agencies to rely on intention-to-treat analyses even if treatment switching results in unrealistic treatment pathways, many agencies have shown a willingness to consider adjustment analyses.[1-3] Simple techniques, such as censoring switchers, should be avoided due to a high chance of bias (see Table 1). Methods like inverse probability of censoring weighting and rank preserving structural failure time model represent an improvement, but

make strong assumptions that aren't easily tested and may seem unrealistic.

The introduction of the estimands framework as part of the upcoming revision of the ICH E9 guideline[4] highlights the limitations of the intention-to-treat approach in an randomized controlled trial setting. Importantly, it provides guidance on how scientific questions can be answered through greater transparency in, and alignment of, clinical trial objectives, design, conduct and analysis. Treatment switching is considered as a type of "intercurrent event" within the revised guidelines—event types which ICH feels deserve greater consideration.

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There is no "standard" analytical approach, such as intention-to-treat, in an observational data setting. Indeed, it's difficult to conceptually apply the intention-to-treat principle in a study that lacks randomization and "allows" for treatment switching. Can we reliably state the *apriori* intention of the treating physician? Observational studies would appear to benefit from adherence to the intercurrent event framework described in ICH E9 (which has strong parallels with HTA's PICOT methodology). However, complex analytical methods such as extensions of inverse probability of censoring weighting and rank preserving structural failure time model are likely to be needed here also.

Big (bad?) data

The use of more sophisticated treatment-switching analytical techniques in order to obtain better (less biased?) treatment comparisons usually requires more data, better data, and greater assumptions. This appears to be borne out in reviews of methods used in observational studies—treatment switching is either ignored or handled by using relatively simple approaches. In defense of this arguably poor showing is that the data required to implement complex methods are not necessarily collected or not consistently measured in real-world clinical practice, resulting in substantial levels of missing data.

Further potential complications abound. Relevant data might come from multiple, independent sources which have collected patient data in different ways, at different times, in different regions, and/or with varying quality. For example, data on treated patients might exist in a drug registry, while untreated patient data might reside in a completely different source. The same patient might appear in more than one data source, potentially leading to double counting. Data sources might need to be linked if, for example, a critical field is present in one source but not in another. The resolution of these sorts of problems often requires the use of techniques such as probabilistic data linkage, especially in cases where health databases don't employ unique patient identifiers (as is the case in most countries, with the Nordics a notable exception). Unsurprisingly to those that have ever attempted it, formally combining independent patient-level health data is a complex exercise, often leading to patchy patient records. The whole can sometimes be less than the sum of the parts!

Table 1: Standard approaches when dealing with treatment switching

Method	Main Assumption
Intention-to-treat analysis	Switching occurs at random
Exclude/censor switches	No confounders that affect both the reason for switching and the treatment outcome
Include treatment as time-varying covariate	No confounders that affect both the reason for switching and the treatment outcome
Inverse probability of censoring weights	No unmeasured confounders
Rank-preserving structural failure time modelling	Randomized groups and common treatment effect
Two-stage model	No unmeasured confounders and existence of a second baseline from which the effect of switching can be estimated

Complexity

There's also the related issue of methodological transparency. Reimbursement authorities tend to have lower levels of comfort in their decision making when faced with higher levels of statistical complexity. Pushing the methodological envelope might lead to less-biased treatment comparisons, but that's of little use if you can't easily convey that message to persons lacking advanced degrees in biostatistics. Reimbursement authorities will struggle to approve what they don't understand. It requires little stretch of the imagination to suspect that this might also be a reason for the lack of use of more sophisticated treatment-switching methods in published observational data studies.

Target trial approach

Adhering to the philosophy of keeping things simple, the target trial approach[5] provides a step-by-step guide for analyzing observational data. The idea is that if we cannot run a randomized controlled trial (for whatever reason), the next best thing is to use observational data to try to emulate the trial that we would have run, if we could have. Importantly, the approach doesn't focus solely on the analytical methods used, which is further reflected in its 7 key components:

- Eligibility criteria
- Treatment strategies
- Assignment procedures
- Follow-up period
- Outcome
- Causal contrasts of interest
- Analysis plan

Used correctly, it can allow appropriate adjustments to be made for treatment switches in observational data. However, in the context of non-random switching, it relies on some of the previously outlined analytical approaches—unbiased estimates of the treatment effect will only be available if there's no unmeasured confounding in the data. Data collection is therefore critical. The success of the target trial approach depends a lot on collecting good quality data on all possible confounders over time. While it's still a relatively untried framework, the target trial is beginning to undergo evaluation in more practical settings.[6-8]

Final thoughts

Treatment switching complicates estimates of comparative effectiveness and is arguably a greater problem in observational studies. While real-world evidence researchers have a wealth of statistical and analytical tools at their disposal, a bigger challenge appears to lie with lack of good quality data.

Alongside improved data collection, general frameworks such as the "estimands" concept and target trial approach offer hope for the improved handling of treatment switching. This should lead to more accurate estimates of comparative effectiveness and, ultimately, better stakeholder decisions.

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Call in the PROs: Giving Credence to the Patient's Perspective in Healthcare Decision Making

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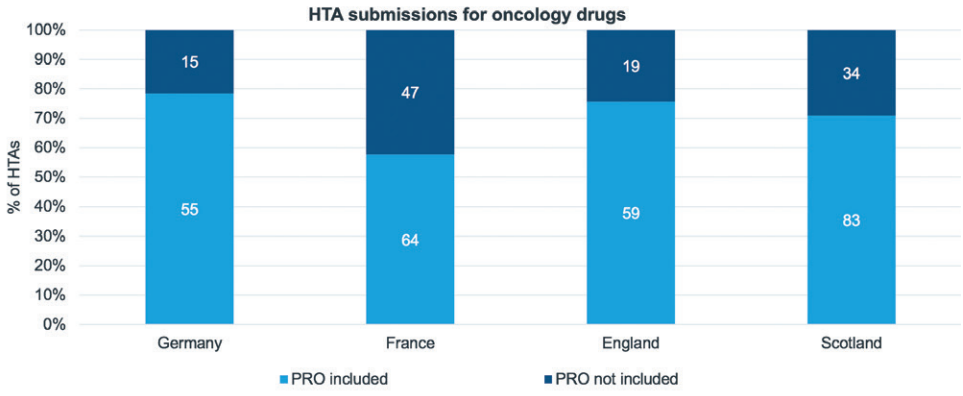
Guidance from HTA bodies should be clearer and more consistent, and to harness the opportunities of PRO data, careful planning and proper execution are needed.

There is a growing movement to incorporate how patients experience treatment into healthcare decision making. In a clinical trial setting, patient experience is measured through clinical outcome assessments (COAs) and in particular, through patient-reported outcomes (PROs), which are a specific type of COA where the report comes directly from the patient.[1] PROs measure the patient experience by asking patients how they feel and function in the context of their disease or condition, and in the context of their treatment.

Regulator interest in PROs goes back a long way, with both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) issuing their first guidance in 2004-2005.[2] The field has matured since then. For example, the EMA has specific guidance on the use of PRO measures in oncology studies,[3] and the FDA recently introduced the "Patient Experience Data" section in their drug review.[4] Consequently, the past decade has shown a marked increase in PRO data included in PRO label claims, particularly in Europe. In a recent survey of health technology assessment (HTA) institutions in the European Union (EU) and Norway, 36 institutions of 48 organizations (75%) reported that they use PRO when estimating effectiveness or safety in their assessments.[5] No distinction was made between disease-specific and generic PRO measures for symptoms, functioning, or health-related quality of life (HRQoL).

PROs have always been important in disease areas where the patient experience is central to the disease definition (eg, pain, autoimmune diseases), but in other therapeutic areas, PROs are less well established. For example, IQVIA analysis of reports by HTA bodies from France, Germany, and the United Kingdom (*Haute Autorité de Santé* [HAS], *Gemeinsamer Bundesausschuss* [G-BA], The National Institute for Health and Care Excellence [NICE], and Scottish Medicines Consortium [SMC] respectively) showed that only 27% of HTA reports in diabetes mentioned PRO data compared to 70% in oncology.[6] Oncology is an interesting case example, as this is a very dynamic field where we see PRO data increasingly being demanded and submitted as part of the evidence package to HTA bodies, yet the response and impact varies greatly from one body to another. Other therapeutic areas

Figure 1. Inclusion of PRO data in HTA submission per country.



Source: IQVIA HTA Accelerator. Scope: Single drug assessments (original, extension of indication, resubmissions) for oncology with a recommendation from Jan 2011 to Dec 2016 from 4 HTA bodies (G-BA, HAS, NICE, SMC).

such as heart failure will likely follow a similar journey, and lessons learned from oncology provide valuable insights in the challenges and opportunities in building a sound PRO strategy.

As mentioned previously, PRO evidence in oncology HTA reports varies across European HTA bodies (Figure 1). Our analysis showed that HAS reports in France mention PRO data less frequently than HTA reports from the independent Institute for Quality and Efficiency in Health Care, (IQWiG), NICE, and SMC in Germany, England, and Scotland, respectively. This is in line with feedback from French payers who consider PRO data as "nice-to-have," albeit figures might be slightly understated due to the fact that HAS assessment reports are less extensive than the publications by G-BA and NICE, which include the manufacturer submission. The impact of PROs on the overall recommendation seems limited: comparing HTA reports that included PRO data versus those that didn't show that drugs with PRO data do not necessarily receive a more favorable recommendation. Only in Germany did we observe higher benefit ratings in HTA reports containing PRO data. When looking specifically into those assessments where PRO data were included, we also saw that in Germany, PRO evidence was mentioned by the payer as being a decision driver far more often than in the other countries (Figure 2). Germany is the only country that explicitly looks at PROs, while other countries will look at PROs as part of the clinical benefit or cost-effectiveness assessment (Table 1).

The German perspective on PROs

New drugs entering the German market are appraised by the G-BA, which generally commissions the IQWiG with the scientific assessment.[7-12] These 2 HTA bodies assess the added benefit of a drug versus the appropriate comparator therapy based on patient-relevant endpoints. The patient-relevant endpoints are categorized in 3 outcome categories: mortality, morbidity, and HRQoL. PROs may offer support for an added benefit against the appropriate comparator in several of these outcome categories, especially in the morbidity area, where symptoms, complications, and adverse events are taken into account.

To determine the added benefit, IQWiG/G-BA look at 2 dimensions: "probability" and "extent of benefit demonstrated" (Table 1).[13] "Probability" indicates the degree of certainty that the results deliver an added benefit with 3 categories: proof, indication, or hint. "Extent of benefit demonstrated" is mainly based on the statistical effect size concerned; ie, explicit inferential statistical thresholds for each benefit category, and the outcome category, eg, all-cause mortality, serious/severe symptoms/adverse events (AEs) and HRQoL, and nonserious/nonsevere symptoms/AEs. HRQoL is grouped with the severe symptoms/AEs category, indicating its importance.

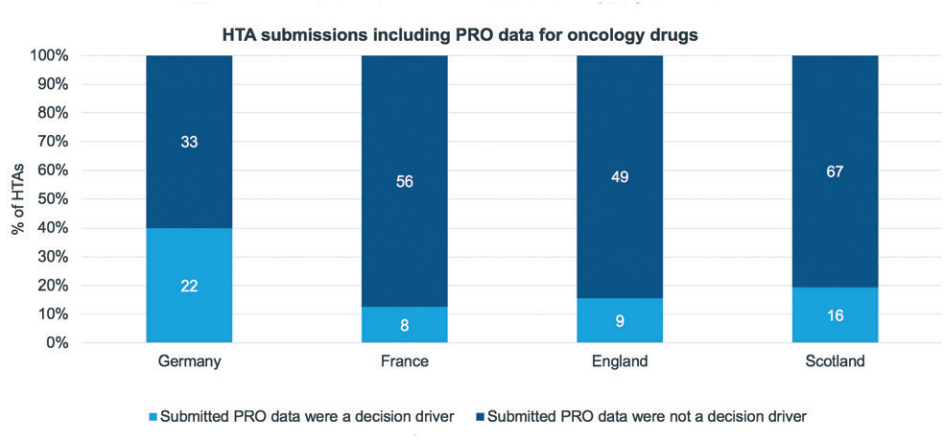
The "extent of benefit demonstrated" can be qualified as major, considerable, minor, nonquantifiable, no added benefit, or less benefit than the appropriate comparator therapy. To obtain an added benefit rating with a PRO (or COA), it is important to use a validated or established instrument, as well as a validated response criterion (minimal important difference [MID]).[14] In case a MID is not available, IQWiG uses the standardized mean difference (expressed as Hedges' g) with an irrelevance threshold of 0.2.[15] This can have serious implications on the IQWiG benefit rating as can be seen in the abiraterone example.

The industry perspective on PROs

While it is generally accepted that PROs are important in oncology, HTA guidance on the handling of PROs in assessments is not detailed and consistent enough for the industry to be able to implement it with a common global approach and strategy. Although Germany applies very specific criteria to assess PRO evidence, not all HTA bodies provide guidance or consistently assess PROs. For example, NICE has detailed guidance for generating health state utilities for cost-effectiveness analysis,[16] but does not cover PROs in relation to measuring patient's HRQoL and functioning.

The varying views of the HTA bodies were also seen in the case study of enzalutamide in men with metastatic castration-resistant prostate cancer not yet indicated for chemotherapy. Enzalutamide's pivotal trial included multiple PRO instruments and the PRO results were generally positive.[17] However, the PRO evidence packages submitted to HTA bodies differed, due to different requirements from the HTA bodies and different experiences of the manufacturer's local teams working on the submissions. This resulted in mixed critique of the submitted PRO data. In Germany, the Brief Pain Inventory (BPI) data were not accepted, as data collection was not consistent between treatment arms; (the difference in available Brief Pain Inventory data was more than 15% between the 2 treatments arms). G-BA did recognize an added benefit based on the median time to deterioration in Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score.[18]

Figure 2. PRO data as a decision driver in oncology HTAs.



Source: IQVIA HTA Accelerator. Scope: Single drug assessments (original, extension of indication, resubmissions) for oncology with a recommendation from Jan 2011 to Dec 2016 from 4 HTA bodies (G-BA, HAS, NICE, SMC).

On the other hand, HAS concluded that the available data were inconclusive as to the effectiveness t of the treatment.[19] Lack of guidance from HTA bodies on PROs leads to several challenges for the industry. IQVIA research showed that the key challenges for collecting PROs lie with choosing the right endpoint and validation of the instrument (Figure 3).

Generating impact with a sound PRO strategy

A sound PRO strategy is needed to generate PRO evidence with impact. Currently, PROs are not consistently included as endpoints in clinical trials, or data are not adequately collected, or presented in an insightful way.

To aid the industry in developing a better PRO strategy, guidance from HTA bodies should be clearer and more consistent. On a European level, there are initiatives for providing better guidance. HRQoL is one of the main categories of endpoints in the EUnetHTA Guidelines for Clinical Endpoints.[20] EUnetHTA guidelines also touch upon the need for HRQoL measures in cost-effectiveness analyses that may also be of value in themselves as clinical assessments.[21] The majority of recent EUnetHTA assessments included PRO data, and in cases where it wasn't included, the lack of PRO data was criticized by EUnetHTA.

A new EU joint HTA structure may provide an opportunity for more consistency and more guidance for collecting PRO data and inclusion of PROs in HTA submissions—but individual HTA bodies should also provide guidance for the assessment of PRO evidence.

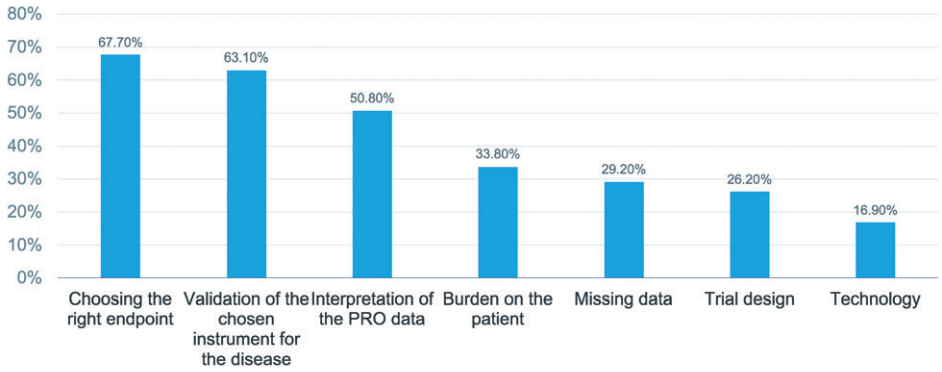
Adding benefit through PROs: a German case study example

The recent assessment of abiraterone for the treatment of metastatic hormone-sensitive prostate cancer is a rich case example that provides both positive and negative learnings in terms of how you should plan for PRO analysis, conduct the study, and analyze the data [IQWiG, March 2018[22-23]]. The study collected multiple PROs, including the Functional Assessment of Cancer Therapy-Prostate (FACT-P), Brief Pain Inventory (Short Form) (BPI-SF), Brief Fatigue Inventory, and EuroQol-5D (EQ-5D). IQWIG accepted the response criteria (ie, MID) of the EQ-5D VAS, FACT-P, and one of the BPI-SF items, but the response criteria of Brief Fatigue Inventory and all other BPI-

Table 1. Overview of remit and use of PROs by HTA bodies in scope

COUNTRY	GERMANY	FRANCE	UK
Agency	G-BA, IQWiG	HAS	NICE, SMC
Possible HTA outcomes	Two outcomes are provided: • Benefit ratings indicate the "extent of benefit demonstrated" compared to the appropriate comparator therapy): - Major - Considerable - Minor - Nonquantifiable - No added benefit - Less benefit • Probability indicates the degree of certainty that the results deliver an added benefit: - Proof - Indication - Hint	Ratings for 2 areas are provided: • Service médical rendu (SMR): actual (clinical) benefit - Important/High (65% reimbursement rate) - Moderate (30%) - Mild/Low (15%) - Insufficient (not included on the positive list) • Amélioration du service médical rendu (ASMR): improvement of actual benefit: - Major (ASMR I) - Important (ASMR II) - Moderate (ASMR III) - Minor (ASMR IV) - No clinical improvement (ASMR V)	NICE: • Recommended • Recommended with restrictions (optimized) • Recommended for use in Cancer Drug Fund • Not recommended SMC: • Recommended • Recommended with restrictions • Not recommended
Impact of HTA outcomes on pricing and reimbursement	Drugs are automatically reimbursed once marketing authorization has been approved. The G-BA benefit ratings influence price negotiations with the National Association of Health Insurance Funds	The SMR determines a new drug's reimbursement rate and the ASMR rating influences the pricing negotiation with the Pricing Committee (Comité économique des produits de santé, CEPS)	• In England, all NICE-approved drugs need to be funded • In Scotland, health boards are required to fund any drug recommended by SMC
Assessment of PROs in HTAs	Submitted PROs are reviewed in patient-relevant morbidity and HRQoL outcomes	Submitted PROs are reviewed as part of clinical benefit	NICE and SMC decisions are primarily based on cost-effectiveness considerations. Submitted PROs are reviewed as part of clinical benefit or used as utility input for cost-effectiveness analyses
PRO guidance for HTA submissions	German HTA bodies apply very specific criteria to assess PRO evidence[12]	No explicit HAS guidance for PROs	NICE and SMC have guidance for generating health state utilities for cost-effectiveness analysis[16,24]

Figure 3. Key challenges for collecting PRO data.
Question: What do you currently see as the top 3 challenges of collecting PRO data? N=62



Source: IQVIA webinar "PROving its worth: How to develop a PRO strategy to distinguish your product with regulators and payers".

SF items were initially not accepted, and because the 95% CI of the standardized mean difference (Hedges' g) was not fully beyond the irrelevance threshold, IQWIG concluded there was no added benefit associated with these endpoints. In response, the manufacturer subsequently submitted many staggered response criteria sensitivity analyses. On one of the Brief Fatigue Inventory items (item 3: measuring worst fatigue), they showed robust effects, which led IQWiG to accept the BFI item 3 response criteria, resulting in a change in IQWiG's rating. This example illustrates that the PRO data had positive effects on the added benefit rating, although it should be noted that overall survival data were available and convincing (ie, significant improvement), which was the key driver in the overall added benefit rating.

Building a convincing case for PROs

A sound PRO strategy starts with a robust understanding of the patient experience within a given disease area and what the patient reports as meaningful benefits. This understanding of the concepts to measure can be developed from a literature review but if high-quality qualitative research has not been published, then researchers should invest early in patient interviews. Robust qualitative evidence supports the PRO strategy with regulatory agencies and argumentation on the severity of measured symptoms/concepts for payers. The target product profile of the drug should include hypotheses for PRO claims and endpoints that address the patient experience, and should be considered early in development to be matured as data becomes available.

PRO instrument selection to measure the concept must be done thoughtfully. Too often these decisions are left late (just before protocol finalization) and the temptation is to adopt an existing instrument or to copy competitors. Researchers selecting instruments that are not appropriate for their context of use, or with designs that are unsuitable for clinical endpoints may be insensitive or see their evidence being rejected by regulatory agencies and payers. Selected instruments should have evidence for their content validity and psychometric properties, or researchers should plan to develop this evidence themselves. Evidence supporting the threshold for clinically meaningful change on the instrument is necessary for endpoints that require a responder definition and to put a statistically significant mean change on the PRO scales into context. Furthermore, endpoints should be pre-specified and alpha-controlled for the best chance of acceptance by regulatory agencies and HTA bodies.

To harness the opportunities of PRO data, careful planning and proper execution are needed. Once a strategy is in place, researchers must ensure they follow through consistently, as poor execution of a PRO strategy in trial operations could result in missing or poor-quality data and suboptimal demonstration of patient benefit. Poor execution of the PRO strategy can lead to payers and regulators dismissing the PRO data or even degrading their rating.

Researchers should further include PRO questions in early scientific advice consultations offered by EMA and EUnetHTA since July 2017. Past HTA advice can prove significant for companies looking for successful strategies and data presentations. For example, in Germany, we can see the need to provide evidence on severity of measured symptoms/concepts. In addition, researchers need to re-think how data are presented to ensure results are understandable and meaningful to all stakeholders. As the importance of PRO data is increasing, this is a great opportunity to prove it with PROs!

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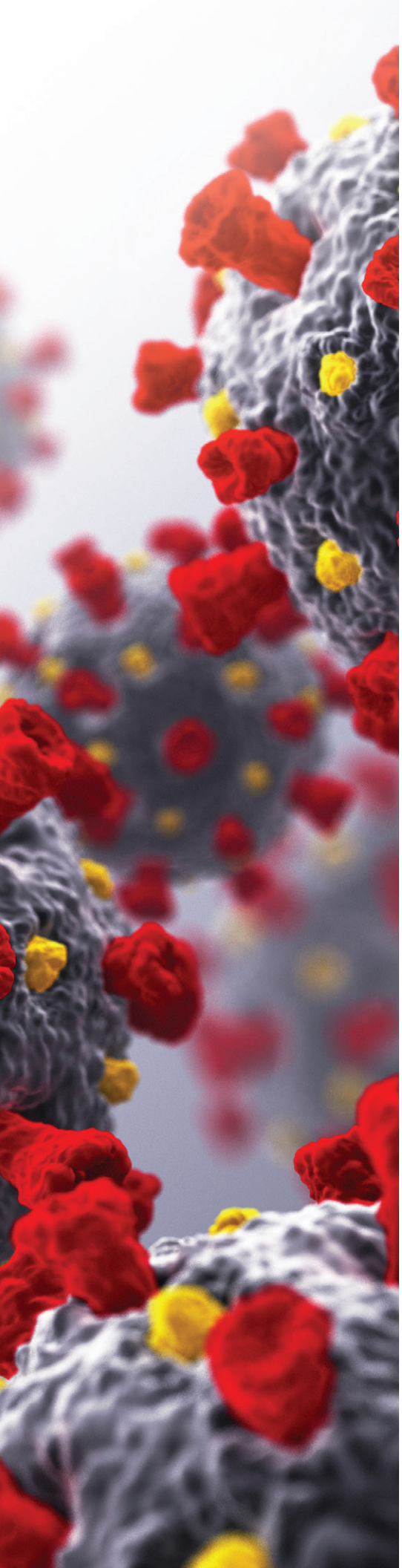

Q&A

COVID-19:

A Global Pandemic—Two Global Perspectives

The Editor-in-Chief and editorial staff worked collaboratively to conduct 2 separate interviews that bring our readers 2 different perspectives on the novel coronavirus pandemic. Our first interview is with **Christian Lindmeier**, spokesperson for the World Health Organization (WHO). Mr Lindmeier provides a global public health perspective on the COVID-19 outbreak, describing the WHO's research agenda in this area, tactics to reduce the spread of the disease, and lessons learned from the Chinese health system.

Our second interview is with **Mirjam Kretzschmar, PhD**, a professor of dynamics of infectious diseases at the University Medical Centre Utrecht, The Netherlands. Her research focuses on developing individual-based modeling approaches to study contact patterns and their relationship with transmission of infection. In the interview, Dr Kretzschmar addresses the uncertainties in modeling and predicting the spread of the coronavirus and discusses ways the HEOR community can contribute to public health decision making about this disease.

Their responses to our questions about the COVID-19 outbreak on the following pages provides unique views from a public health and an outcomes researcher's (namely disease modelling) perspective.

Interview With Christian Lindmeier

Spokesperson for the World Health Organization, Geneva, Switzerland

"Since the beginning of the outbreak, the WHO continues to coordinate the global response, through country and regional offices and headquarters, by shedding light continuously on ... key areas."

VOS: How reliable are the data regarding overall infection rates reported by countries that traditionally keep information close to the vest and that do not usually seek help from outside organizations such as WHO? In light of the epidemiological data on hand to date, do you have any insight into why this disease has spread more rapidly in some countries versus others?

Lindmeier: The WHO requests that national authorities report probable and confirmed cases of novel coronavirus COVID-19 infection within 48 hours of identification, through the National Focal Point and the Regional Contact Point for International Health Regulations at the appropriate WHO regional office. Reporting of case-based reports is requested as long as it is feasible for the country. When it is not feasible to report case-based data, countries are requested to provide daily and weekly aggregated data.

We fully recognize that affected countries are under great pressure to respond to the outbreak and the WHO continues to encourage them to share the data we need, but this is not because of a lack of transparency from their side. It is directly linked to the emergency situation and the logistical challenges countries face to collect those data.

We're communicating with ministers directly and we urge all countries to share these data with the WHO immediately.

VOS: What does it take to classify a disease outbreak as a pandemic, and what is the impact to the global community?

Lindmeier: A pandemic is the worldwide spread of a new disease. An influenza pandemic occurs when a new influenza virus emerges and spreads around the world, and most people do not have immunity. Viruses that have caused past pandemics typically originated from animal influenza viruses.

For both seasonal and pandemic influenza, the total number of people who get severely ill can vary. However, the impact or severity tends to be higher in pandemics in part because of the much larger number of people in the population who lack pre-existing immunity to the new virus. When a large portion of the population is infected, even if the proportion of those infected that go on to develop severe disease is small, the total number of severe cases can be quite large.

VOS: Can you provide examples of recent tactics that the WHO has employed to help control the spread of the virus and to help educate healthcare workers and the public to prevent further transmissions?

Lindmeier: Since the beginning of the outbreak, the WHO continues to coordinate the global response, through country and regional offices and headquarters, by shedding light continuously on the following key areas:

- Increasing understanding of the disease. The WHO is constantly analyzing data as we receive it and working closely with global experts on a range of topics. WHO is proposing specific studies to better understand transmission, risk factors, and source of the infection. Some of these studies are already underway.
- Providing advice to countries on critical preparedness, readiness and response actions for COVID-19, and to individuals on how to protect themselves and others, including on the safe home care for patients with suspected COVID-19 infection. The advice includes protecting others from coughs and sneezes, hand cleaning, food safety, and best practices at markets. We are also covering travel and international traffic in relation to the outbreak of the novel coronavirus COVID-19. Finally, we are advising businesses and employers to make sure they implement containment measures at workplaces.
- Keeping countries and the general public informed. The WHO is informing the public through daily situation reports and dashboards, such as the WHO Health Emergency Dashboard, and the WHO Novel Coronavirus (COVID-19) Situation Dashboard, that are displaying data in real time.
- Coordinating with partners. The WHO is working with our networks of researchers and other experts to coordinate global work on surveillance, epidemiology, forecasting, diagnostics, clinical care and treatment, and other ways to identify and manage the disease and limit onward transmission.
- Healthcare workers are at the front line of any outbreak response and as such are exposed to hazards that put them at risk of infection with an outbreak pathogen (in this case COVID-19). Hazards include pathogen exposure, long working hours, psychological distress, fatigue, occupational burnout, stigma, and physical and psychological violence. Facilities should familiarize personnel with technical updates on COVID-19 and provide appropriate tools to assess, triage, test, and treat patients and to share infection prevention and control information with patients and the public.

VOS: Can you summarize the discussions and overall direction from the WHO's recent forum in plotting a research agenda for the virus? How can the HEOR community contribute to the research agenda and to the WHO's R&D Blueprint?

Lindmeier: Following the recommendations of the Emergency Committee, Tedros Adhanom Ghebreyesus, PhD, MSc, the WHO Director-General, met with world scientists at WHO's Geneva headquarters from 11-12 February 2020 to assess the current level of knowledge about the new COVID-19 virus, agree on critical research questions that need to be answered urgently, and ways to work together to accelerate and fund priority research that can contribute to curtail this outbreak and prepare for future outbreaks.

There are currently over 200 clinical trials registered on the Chinese clinical trials registry, testing a variety of interventions with a variety of endpoints. Outside of China, there is a global data platform facilitated by the WHO with the goal of producing a global cohort of hospitalized patients. Clinical characterization protocols are available to inform sampling strategies and sharing. A number of large-scale randomized trials are being planned, both inside and outside China. Epidemiologic studies as conducted by public health authorities have been conducted by the relevant groups in the United States, Europe, and other regions with exported cases.

Prioritization activities for which interventions to study, so as to optimize the outcome of individual patients, from antivirals to immunomodulators to supportive care interventions, are ongoing. In addition, work to coordinate research is ongoing, with the hoped-for standard data variable and outcome collection by a variety of international networks. Most importantly is ensuring adequate coordination of these efforts to achieve useable results across regions.

See R&D roadmap for more information on R&D priorities: https://www.who.int/blueprint/priority-diseases/key-action/Roadmap-version-FINAL-for-WEB.pdf?ua=1.

VOS: Please discuss the progress in developing a vaccine for COVID-19. Because so many companies are scrambling to develop and test vaccines, is there concern that the vaccine may not be clinically effective in the treatment of the disease? What are some of the risks to the public with vaccines developed under this kind of accelerated schedule?

Lindmeier: The WHO has received applications for review and approval of more than 40 diagnostic tests. More than 41 vaccines are in development and many clinical trials of therapeutics are underway. We expect the initial results within a few weeks.

A master global clinical trial protocol for research and prioritization of therapeutics is ongoing at the WHO. The WHO is preparing a landscape analysis of the vaccine and therapeutic investigational candidates that could be used against COVID-19 and will work on an evidence-based framework to transparently select the most promising/advanced therapeutics and vaccines candidates to move forward for clinical evaluation. We will convene meetings to discuss all critical steps that are required (eg proof-of-concept, preliminary safety data, regulatory expectations) ahead of planning for efficacy trials as well as key epidemiological and clinical aspects that we must learn and that will help enlighten vaccine and treatment development.

VOS: Overall, what can we learn from the way the affected countries have reacted to the COVID-19 epidemic?

Lindmeier: I quote WHO Director-General, Dr Tedros Adhanom Ghebreyesus, who said, "China and other countries are demonstrating that spread of the virus can be slowed and impact reduced through the use of universally applicable actions, such as working across society to identify people who are sick, bringing them to care, following up on contacts, preparing hospitals and clinics to manage a surge in patients, and training health workers. WHO calls on all countries to continue efforts that have been effective in limiting the number of cases and slowing the spread of the virus. Every effort to contain the virus and slow the spread saves lives. These efforts give health systems and all of society much-needed time to prepare, and researchers more time to identify effective treatments and develop vaccines. Allowing uncontrolled spread should not be a choice of any government, as it will harm not only the citizens of that country but affect other countries as well."

Interview With Mirjam Kretzschmar, PhD

Infectious Disease Modeler, University Medical Centre Utrecht, The Netherlands

"There is a big challenge here for the HEOR community to analyze the economic aspects of this crisis and to contribute with insight about the economic impact and societal costs of this crisis."

VOS: Can you briefly explain what the COVID-19 virus is and how it relates to SAR-CoV2 or to influenza type A, particularly with respect to its transmission rate and probability of having severe outcomes?

Kretzschmar: COVID-19 is the disease caused by the new coronavirus SARS-CoV-2. The virus emerged at the end of 2019 in Wuhan, China, and has since spread all over the world. It is believed that the virus was transmitted from animals to humans and was then able to spread from human to human. It is related to the SARS-CoV virus, which caused the outbreak of SARS in 2003. However, it is less lethal than SARS, but has a higher transmissibility. At this time, it is not yet possible to give a reliable estimate of the probability of having a severe outcome due to limited testing and limited knowledge of the extent of transmission in populations. We do know, however, that risk of severe outcomes increases with age. The influenza virus is a different virus, not related to coronavirus. Epidemiologically, the situation for influenza is different, because most people have at least some partial immunity, there is a vaccine, and medication available for treatment.

VOS: How reliable are the data regarding overall infection rates reported by countries that traditionally keep information close to the vest and that do not usually seek help from outside organizations such as WHO? In light of the epidemiological data on hand to date, do you have any insight into why this disease has spread more rapidly in some countries versus others?

Kretzschmar: That is hard to say. Even in countries that do report openly, there is a large uncertainty due to limited testing. More reliable at the moment are hospitalization data and numbers of patients needing treatment in an intensive care unit. It is unclear why there seem to be differences between countries in epidemic spread. Possible reasons are differences in contact patterns, but also differences in testing and reporting due to different healthcare systems may play a role. Finally, the epidemics in various countries were seeded at different moments in time and might therefore be at different points in the exponential growth curve.

VOS: What are the key parameters affecting the rate at which the disease spreads across a population? What determines when the rate of occurrence of new cases starts to decline?

Kretzschmar: The key parameters are contact rates and intervention effectiveness (eg, time to diagnosis and isolation of cases, effectiveness of contact tracing). The effectiveness of interventions is influenced by the proportion of cases who remain asymptomatic or who have only mild symptoms. These persons do not get diagnosed and reported to the healthcare

system, but they might contribute to further transmission, although we do not yet know what their infectivity may be. Given the importance of contact rates for epidemic spread, the most important intervention at present is social distancing. If social distancing is effective in reducing contacts to a minimum, transmission can be reduced to very low levels. It will then take around 1 to 2 weeks before effects can be seen in the numbers of new cases. Alternatively, once a substantial proportion of the population is immune, numbers of cases will start to decline.

VOS: Are there still some key uncertainties in modeling or predicting the spread of the coronavirus? If so, what are they, and do you think we will have better information about them soon?

There are many uncertainties: Proportion of asymptomatic and mild infections, how much transmission takes place before symptom onset, how much do asymptomatic persons contribute to transmission, is there immunity after recovery and how long does it last, how effective is social distancing in reducing transmission, all these factors are uncertain. In mathematical models, we need to use assumptions based on insights gained from the outbreak in China and other studies that are now published daily in scientific journals or on preprint servers. The time up to now has been too short for conducting rigorous clinical and epidemiological studies.

VOS: Do you know how much, and in what ways, the HEOR community has been able to contribute to public health decision making about this disease?

Kretzschmar: Up to now, decisions have been mainly based on the aims of outbreak containment and mitigation. These decisions to implement rigorous measures of social distancing have major economic impact, which will have implications on a longer time scale. There is a big challenge here for the HEOR community to analyze the economic aspects of this crisis and to contribute with insight about the economic impact and societal costs of this crisis. Much more work on these aspects needs to be done in the future, also for supporting decision makers once the epidemiological urgency has subsided.

VOS: Is there anything that I haven't asked you that you feel our readers should know?

Kretzschmar: Last week Ferguson, et al from the Imperial College in London, England, published a paper where they predicted the implications of the COVID-19 outbreak for the United Kingdom and the United States based on a modelling study. They used a very detailed individual-based model that took many factors such as geographic and demographic distributions into account. They analyzed the possible impact of a variety of intervention scenarios and came to the conclusion that the only possible strategy at present is suppression of further transmission if we want to prevent an overload of the health system capacities. Although many uncertainties remain, this modelling study is at present one the best we have for assessing the possible impact of interventions. The results of Ferguson's study are in line with other modelling studies published to date. As new data become available to improve parameter estimates, better predictions may be possible. We now need better data on some of the key clinical parameters, but also on the effectiveness of social distancing measures as applied in many countries.

Prevention starts with 10 basic things people can do:

1. Clean your hands regularly with an alcohol-based hand rub or wash them with soap and water.
2. Clean surfaces (eg, kitchen benches and work desks) regularly with disinfectant.
3. Educate yourself about COVID-19. Make sure your information comes from reliable sources.
4. Avoid traveling if you have a fever or cough, and if you become sick while on a flight, inform the crew immediately. Once you get home, contact a health professional and tell them about where you have been.
5. Cough or sneeze into your sleeve or use a tissue. Dispose of the tissue immediately into a closed rubbish bin, and then clean your hands.
6. Take extra precautions to avoid crowded areas if you are over 60 years old, or if you have an underlying condition.
7. If you feel unwell, stay at home and call your doctor or local health professional.
8. If you are sick, stay at home, and eat and sleep separately from your family. Use different utensils and cutlery to eat.
9. If you develop shortness of breath, call your doctor and seek care immediately.
10. It's normal and understandable to feel anxious, especially if you live in a country or community that has been affected. Find out what you can do in your community. Discuss how to stay safe with your workplace, school, or place of worship.

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